UNIVERSIDADE DE LISBOA

Faculdade de Medicina de Lisboa

LATER STAGES OF PARKINSON'S DISEASE

Miguel Vilhena Soares Coelho

Orientadores:

Professor Doutor Joaquim José Coutinho Ferreira

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Tese especialmente elaborada para obtenção do grau de Doutor em Medicina, Especialidade de Neurologia

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"Published since September 1843 to take part in a severe contest between intelligence, which presses forward, and an unworthy, timid ignorance obstructing our progress."

The Economist

Aos meus pais, por todas as oportunidades dadas.

Ao Matias, Diogo e Francisco, o meu futuro.

À Ana.

ABSTRACT

Parkinson`s disease (PD) is an age-related neurodegenerative disorder with progressive disability. Its incidence is expected to increase substantially owing to ageing of world population. Better general healthcare, and better understanding of complications and clinical management of PD is likely to increase in the future the prevalence of PD patients in very advanced stages of disease, when disability is most severe. These very advanced patients will represent an important burden for families and the healthcare and social systems, and a new challenge for healthcare personnel. Nevertheless, the clinical characteristics of these late-stage PD (LS-PD) patients have been only partially described in the pre-levodopa or post-levodopa era. Since knowledge of the health needs of these patients is crucial to plan effective health resources that cover patients and caregivers needs, we aimed to study the clinical features and handicap of LS-PD patients attending two tertiary centres, selected on the basis of motor disability. We also aimed to study whether the handicap of LS-PD patients differs from that of classical advanced stage PD patients, i.e., patients manifesting disabling levodopa-induced motor complications, and, if so, whether that modifies the way we conceive today the natural history of PD. Finally, we reviewed the pharmacological and non-pharmacological interventions available to treat the non-motor symptoms of LS-PD, using a systematic approach.

Participants were LS-PD (stage 4 or 5 of Hoehn & Yahr scale in *on* state) and advanced stage PD patients (patients with disabling levodopa-induced motor complications selected to deep brain stimulation), and their informal caregivers. Cross-sectional data were obtained using comprehensive clinical assessment. Handicap was assessed using the London Handicap Scale (LHS). Descriptive and regression analysis was performed. To review the treatment available for non-motor symptoms in LS-PD, we extracted the controlled clinical trials for PD dementia, psychosis, falls, bone fractures, joint and skeletal deformities, pain, orthostatic hypotension, gastrointestinal abnormalities and urological dysfunction; we chose these symptoms because they were considered as the most disabling for LS-PD patients, based on our results and published data.

50 LS-PD patients (mean age 74.1 years and mean disease duration 17.9 years) were studied. Severe akinetic symmetric parkinsonism was present in most, with negligible rigidity and tremor, and most patients were wheelchair-bound. Postural instability and freezing of gait, causing frequent falls and fractures, and prominent dysarthria and

dysphagia dominated the motor syndrome. Levodopa, used as monotherapy in one-third of the cases, remained partially effective in most patients but with limited clinical relevance. Dosage of antiparkinsonian drugs was probably influenced by the frequent occurrence of neuropsychiatric symptoms. Motor fluctuations and dyskinesias were frequent but not disabling. All had neuropsychiatric and dysautonomic symptoms, namely dementia and visual hallucinations in half and depression in two-thirds of the patients. Lack of tremor and absence of depression were independently associated with dementia. Greatest impact on perceived health status was due to motor and non-motor levodopa-resistant symptoms. The LHS was easy to use in these patients and their caregivers. Handicap was severe and determined by dementia, behavioural complaints and the severity of non-dopaminergic motor features. Most affected domain of handicap was Orientation. Co-morbidities and past medical conditions were frequent. Patients visited doctors infrequently and made low use of health resources, while unpaid caregivers reported a high burden which correlated with patients' handicap. The LHS was also easily completed by 100 advanced stage PD patients (mean age 61 years and mean disease duration 12.2 years) and their carers. Handicap was moderate-to-severe, although less than that of LS-PD patients. In contrast to the latter, Physical Independence and Social Integration were the most affected domains, and the determinants of handicap were disability in ADL and dyskinesias.

The clinical features, severity and determinants of handicap of PD patients in late-stage differ from those in advanced stage, although they are nowadays classified under the generic category of *advanced stage* patients. LS-PD patients are severely handicapped from axial motor and non-motor symptoms unresponsive to levodopa, and they are very dependent on caregivers. Data suggest that LS-PD is a very distinct sub-group of advanced stage PD, and we propose an operational definition for LS-PD that anchors on (lack) of functionality regardless the cause is motor or non-motor symptomatology, using the Schwab and England scale in *on*. Unfortunately, few controlled clinical trials are available to treat most non-motor symptoms that disable LS-PD patients. Best evidence exists for the treatment of dementia, psychosis, osteoporosis and prevention of fractures, and sialorrhea.

The present study provides cross-sectional evidence that LS-PD is a distinct sub-group of advanced stage PD, and that LS-PD patients manifest a clinical picture dominated by a severe akinetic symmetric non-dopaminergic motor phenotype and by severe non-motor features, which are overall poorly responsive to levodopa. LHS is easily completed by PD patients and handicap can be further explored as a patient-centred outcome in PD. Caregivers have a high burden that is correlated with patients' handicap. In face of an expected increase in the prevalence of LS-PD and lack of efficacious therapies for most disabling symptoms, future research and allocation of funds should focus on non-levodopa responsive aspects of the disease and the needs of caregivers.

Key-words: Parkinson's disease; late stage; advanced; handicap; dementia

RESUMO

A doença de Parkinson (DP) é uma doença neurodegenerativa cuja incidência aumenta com a idade, e prevê-se que a sua prevalência aumente no futuro devido ao envelhecimento da população mundial. O aumento da esperança de vida, as melhores condições gerais de saúde e o melhor entendimento e tratamento actual da DP serão também responsáveis pelo fututo aumento do número de doentes com DP que se encontram nas fases mais avançadas da doença. Os doentes na fase tardia da DP (LS-PD) estão muito incapacitados, sobretudo pela ocorrência de sintomas motores e não motores que respondem mal à levodopa. Esta população de doentes será uma sobrecarga muito grande para os seus cuidadores, para o sistema de saúde e da segurança social, e ainda um desafio para os técnicos de saúde que estão pouco habituados e habilitados a manejar estes doentes. Apesar do acima exposto, as características destes doentes são mal conhecidas e pouco reportadas na literatura das eras pré- e pós-levodopa. No entanto, o planeamento dos recursos de saúde e sociais a alocar a estes doentes e seus cuidadores exige um conhecimento preciso e substancial das suas características clínicas, da causa da sua incapacidade, da forma como são tratados hoje em dia e usam o sistema de saúde, e de quais as actuais intervenções terapêuticas eficazes nesta população de doentes.

Foi nosso propósito estudar as características clínicas e a incapacidade ("*handicap"*) de uma população de doentes LS-PD consultados em 2 clínicas de movimento de hospitais terciários, recrutados com base na sua incapacidade motora. Adicionalmente, tivemos por objectivo averiguar se a intensidade e causa da incapacidade destes doentes difere daquela dos doentes classicamente referidos como estando em estádio avançado, isto é, doentes com complicações motoras incapacitantes induzidas pela levodopa, e, a ser verdade, se tal mudaria a forma como entendemos hoje a história natural da DP. Por último, revimos de forma sistematizada qual a eficácia e segurança das intervenções farmacológicas e não-farmacológicas para tratamentos dos sintomas não motores da LS-PD.

Participaram neste estudo doentes LS-PD (doentes em estádio 4 ou 5 de Hoehn e Yahr em *on*), doentes em estádio avançado (doentes com complicações motoras incapacitantes induzidas pela levodopa e seleccionados para estimulação cerebral profunda), e os seus cuidadores. Procedeu-se a uma colheita transversal dos dados, usando um questionário

semi-estruturado, escalas apropriadas, o exame objectivo e recorrendo aos processos clínicos em caso de dúvida ou omissão de dados. O *handicap* foi medido usando a London Handicap Scale (LHS). Fez-se uma análise descritiva dos dados e modelos de regressão. Para a revisão das intervenções terapêuticas, procedeu-se a uma extracção dos ensaios clínicos controlados nas seguintes indicações: demência associada à DP, psicose, quedas, fracturas ósseas, deformidades músculo-esqueléticas, dor, hipotensão ortostática, patologia gastro-intestinal e urológica. Estes sintomas foram escolhidos por acharmos serem os mais incapacitantes para os doentes LS-PD, com base nos nossos resultados e os já publicados.

Foram incluídos 50 doentes LS-PD (média de idade 74.1 anos e média de duração de doença de 17.9 anos). O quadro motor foi caracterizado por um parkinsonismo grave, simétrico e acinético, quase sem rigidez ou tremor. Os sintomas motores axiais foram predominantes, com disfagia em 68% dos doentes e gastrostomia em 10%, disartria grave em quase todos, e *freezing* da marcha em 62% e quedas em metade, causando 20% de fracturas nos últimos 5 anos. 78% dos doentes necessitavam de cadeira de rodas. A pontuação média em *on* na UPDRS parte motora foi de 49.18 pontos. A levodopa foi usada em monoterapia em 1\3 dos doentes, e foi considerada pelos doentes como parcialmente eficaz, embora esse benefício não tivesse relevância clínica. A dose baixa dos agentes antiparkinsónicos foi possivelmente influenciada pela frequência elevada de sintomas cognitivos e comportamentais. As flutuações motoras ocorreram em 78% dos doentes e as discinésias em 62%, mas não foram incómodas. Os sintomas não motores foram universais, a depressão ocorrendo em 62% e a apatia e a ansiedade em metade dos doentes, a demência em 50% e as alucinações em 44%, enquanto que a obstipação afectou 82% dos doentes, a disfunção urinária 62% e a hipersudorese um terço. A ausência de tremor e de depressão foram os maiores determinantes da presença de demência (R^2 = 45%; $p < 0.01$). Os sintomas que maior impacto tiveram na percepção do estado de saúde dos doentes foram os sintomas motores axiais e os sintomas não motores, resistentes à levodopa. A LHS foi facilmente compreendida e preenchida pelos doentes e cuidadores. A sua pontuação média total (0 = *handicap* máximo; 1 = ausência de *handicap*) foi de 0.33 (SD±0.15), e o seu domínio mais afectado o da Orientação. A presença de demência, a pontuação na parte I da UPDRS (sintomas cognitivos e

comportamentias) e a pontuação do estádio Hoehn e Yahr em *off* foram os maiores determinantes do *handicap* (R^2 ajustado = 0.62; p = 0.000). Os doentes LS-PD tinham um elevado número de co-morbilidades e de doenças anteriores. 70% dos doentes viviam na sua casa e 16% estavam institucionalizados, enquanto que 38% tinham um cuidador pago. Nos 6 meses precedentes, tinham consultado em média o médico de família 2.2 vezes (incluíndo consultas somente para prescrição) e o neurologista 1.7 vezes (incluíndo consultas somente para prescrição); 20% faziam fisioterapia e 6% faziam terapia da fala ou usufruiam de enfermagem ao domicílio. Os cuidadores informais destes doentes relataram uma grande sobrecarga: por semana passavam em média 5 dias (significando 5 dias x 24h) cuidando dos seus familiares, e reportaram que o impacto médio que a DP tinha nas suas vidas era de 3.5 (0 = sem impacto; 4 = impacto máximo). A sua sobrecarga estava fortemente correlacionada com o *handicap* dos doentes, sobretudo com os domínios Orientação e Mobilidade. A LHS foi também facilmente compreendida e preenchida por 100 doentes em estádio avançado (média de idade 61 anos e média de duração de doença de 12.2 anos) e pelos seus cuidadores. A pontuação total média da LHS foi inferior à dos doentes LS-PD (0.56 (±0.14)), e os domínios mais afectados o da Independência Física e da Integração Social. Os maiores determinantes de *handicap* foram a pontuação média da MDS-UPDRS parte II (aspectos motores das actividades de vida diária) em *off* (p = 0.020), a pontuação média na escala de Schwab e England (independência funcional nas actividades de vida diária) em *off* (p = 0.020) e *on* (p = 0.05), e a pontuação média na escala modificada de AIMS em *on* (p = 0.042) (escala de discinésias) (R^2 = 29.6%).

As características clínicas, a gravidade e determinantes de *handicap* dos doentes LS-PD são muito distintas daquelas dos doentes em estádio avançado, embora hoje em dia sejam classificados na categoria genérica de doentes *em estádio avançado.* Os doentes LS-PD estão gravemente incapacitados por sintomas motores axiais e sintomas não motores pouco respondedores à levodopa, e estão muito dependentes dos seus cuidadores. Os nossos dados e de outros sugerem que os doentes LS-PD constituem um sub-grupo muito diferente dos doentes em estádio avançado, e nós propomos uma definição operacional para LS-PD ancorada na (perda) independência funcional dos doentes nas actividades de vida diária, medida pela escala de Schwab e England em *on*, seja ela causada por manifestações motoras ou não motoras. Infelizmente para estes

doentes, encontrámos muito poucos ensaios clínicos controlados que mostrassem a eficácia de intervenções farmacológicas ou não farmacológicas para tratar os sintomas não motores que mais incapacitam estes doentes. A evidência mais robusta é para o tratamento da demência associada à DP (rivastigmina), da psicose (clozapina), da osteoporose e prevenção de fracturas (alendronato, risedronato, 1α-hidroxi-vitamina D3) e da sialorreia (toxina botulínica, serotipos A e B).

Os resultados transversais do presente estudo mostram que a LS-PD é um sub-grupo distinto dos doentes em estádio avançado da DP, e que os doentes LS-PD têm um quadro clínico dominado por um fenótipo motor não-dopaminérgico com grande acinésia simétrica e graves sintomas axiais, e por sintomas não motores graves, os quais de forma geral não respondem ou respondem pouco à levodopa. A LHS é facilmente compreendida e preenchida por doentes com DP e seus cuidadores, e o *handicap* poderá no futuro ser mais explorado na DP como uma medida centrada no doente. Os cuidadores destes doentes têm uma grande sobrecarga que está correlacionada com o *handicap* dos seus familiares. Face ao previsível aumento da prevalência de doentes com LS-PD e à ausência actual de intervenções terapêuticas eficazes para a maioria dos seus sintomas mais incapacitantes, a investigação e alocação de verbas futuras devem focar-se nas manifestações da DP não respondedoras à levodopa e nas necessidades de saúde dos cuidadores.

Palavras-chave: doença de Parkinson; estádio avançado; incapacidade; demência; tratamento

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INTRODUCTION

Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder characterized by neuronal loss of the dopaminergic neurons of the substantia nigra (SN) pars compacta (SNpc), particularly in its lateral ventral tier, associated with Lewy pathology.[1-4] However, extranigral neuropathology of the cholinergic, noradrenergic and serotonergic systems has also been well documented.[1-3] Lewy pathology is typified by Lewy bodies, which are round α-synuclein immunoreactive eosinophilic inclusions in neuronal perikarya, mostly found in the SNpc.[1,2,5,6] Lewy pathology is also found in extranigral regions of the central nervous system, such as the pons, basal forebrain, limbic cortex or higher order association cortices and additionally in the peripheral autonomic nervous system.[2,7-9]

The primary cause of PD is still unknown but the concept of PD as a single nosological entity is changing to a broader definition that includes different conditions with a common clinical final pathway.[10] Nevertheless, there is extensive new information regarding the aetiology and pathogenesis of PD.[11] Environmental exposure, namely to pesticides, has been suggested to increase the risk of developing PD.[12-17] On the other hand, there is a growing number of gene mutations causing monogenic PD (SNCA, PRKN, PINK1, DJ-1 and LRRK2).[18-26] Whatever the cause of nigral degeneration and formation of Lewy bodies, recent evidence shows that pathologic (misfolded) α-synuclein may possibly spread from affected to unaffected cells in a prion-like manner, namely from the gut to the brain via the vagal nerve, supporting the hypothesis that PD may be a prion-like disease.[27,28]

PD is the second most common age-related neurodegenerative disorder after Alzheimer's disease. PD occurs worldwide with an age-adjusted prevalence of 1.8% and similar incidence in females and males.[29] Interestingly, a recent door-to-door survey conducted in the Portuguese population aged ≥ 50 years-old found an adjusted prevalence of 0.24% and an estimative of the total number of PD cases in Portugal of 180/100.000 inhabitants (Nilza Gonçalves, Joaquim J Ferreira, personal communication, February 26, 2015). The mean age of onset is 65 years, with prevalence rising from 0.6% at age 65–69 to 2.6–3.5% at age 85–89.[29,30] Disability is progressive and associated with increased mortality (relative risk of death 1.6–3.0 compared with control populations), although considerable heterogeneity exists between studies.[8,31,32]

The classical motor features of PD are an asymmetrical bradykinesia, lead pipe type rigidity and a 4-6 Hz pill-rolling rest tremor, as well as postural instability later in the disease course.[33] However, non-motor symptoms (NMS) such as dysautonomia, pain, sleep disturbance, depression, psychosis and dementia are now well established features of PD and they increase in frequency and severity in later stages of disease.[34] The pharmacological and surgical therapies substantially improve motor symptoms, but it becomes more difficult to achieve satisfactory symptomatic control once patients reach a more advanced disease stage. Levodopa (L-dopa) remains the "gold-standard" antiparkinsonian drug but its long-term use is associated with the development of disabling motor complications, which occur in up to 80% of PD patients.[33,35-39] These L-dopa-induced motor complications (MC) are difficult to treat and impair quality of life (QoL) of patients.[40] As a rule, NMS do not benefit much with L-dopa and we still lack effective treatments for most NMS.[41]

Progression and staging of Parkinson's disease

Progression

Classically, and once motor symptoms are manifest, the natural history of PD is regarded as the emergence of L-dopa-induced MC and the progression in severity of motor symptoms.[39,42] Most attention has been given to MC. Indeed, the development of L-dopa-induced MC is a distinctive marker of PD which was soon noted after the introduction of L-dopa to treat parkinsonism.[43,44] Most PD patients will develop L-dopa-induced MC, namely motor fluctuations and dyskinesias, after an initial phase of sustained and smooth response to dopaminergic drugs.[39,45,46] The frequency of MC vary considerably, however Ahlskog and Muenter[39] have found an overall frequency of MC of about 40% after 4-6 years of L-dopa treatment. The emergence of MC is of paramount importance due to their impact on patients' disability and QoL, caregivers' burden and a cause of complex drugs regimens.[47-50] In fact, MC are the major indication for advanced therapies in the management of PD, such as functional surgery, apomorphine infusion and L-dopa\carbidopa intestinal gel pump. Due to their relevance, MC have been a widely accepted criterion to define the onset of *advanced stage* in the progression of PD, and much knowledge has been accumulated about MC.[39,45,46,51-53] The clinical progression of PD is also characterized by an increase in severity of motor symptoms. These motor

symptoms can be either L-dopa-responsive or L-dopa-resistant.[54,55] Only recently more attention has been focused on motor symptoms resistant to L-dopa, which are mostly axial in nature such as dysphagia, dysarthria, postural instability and falls.[56] However, in more advanced PD stages, when disability is most severe, symptoms that are resistant to L-dopa seem to contribute more to patients' disability than MC. [42,56-59] In some patients, MC may even remit in later disease stages independently from a reduction in the dose of antiparkinsonian drugs.[56,59]

In contrast to the classical view, plenty of evidence now shows that NMS increase in frequency and severity with disease progression.[34,56,60-63] For the most part, these NMS are resistant to L-dopa.[41] Thus, non-motor and axial symptoms not improved by L-dopa, such as dysautonomia, sleep disturbances, dementia, psychosis, apathy, postural instability and falls increase in frequency and severity with longer disease duration, and they dominate the clinical picture and are the major determinants of patients' disability in more advanced stages of PD.[56-58,64-66] In fact, the strongest independent predictors of institutionalization and death are dementia, hallucinations, postural instability and falls.[56,67-72] Additionally, the advent of deep brain stimulation (DBS) to treat MC in the last 25 years has substantially improved the management of these motor symptoms,[73-75] but unfortunately it is of little help to treat motor and non-motor symptoms resistant to L-dopa.[76-78] Thus, the classical model of PD progression does not incorporate motor and non-motor symptoms resistant to L-dopa, which end up dominating the clinical picture of PD as disease progresses.

Indeed, the pathology model of PD progression in 6 stages by Braak *et al*[1] gives a biological rationale for the increase of axial motor and non-motor symptoms resistant to L-dopa with the clinical progression of PD. The pathological process begins in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus, and then gradually ascends through the brainstem, anteromedial temporal mesocortex and finally the neocortex, thus progressively affecting more brain regions involved in axial symptoms and NMS, and more non-dopaminergic systems.[1]

Staging

As a progressive disorder, attempts have been made since long ago to stage the clinical evolution of PD.[42] Nevertheless, clear-cut and standard definitions of the different stages of PD are still lacking, and even experts disagree between them. Usually, the natural

history of PD is divided into a *Prodromal stage, an Early stage,* an *Intermediate or Moderate stage and an Advanced stage*, according to the presence and severity of motor symptoms, the overall benefit from antiparkinsonian drugs and the emergence of MC.[42,45,51,52,79,80] There is no available definition for *late-stage* PD today. The most widely used and accepted definition for *advanced stage* is the onset of L-dopa-induced MC or, alternatively, when MC become severe enough to substantially impair patients' independence in the activities of daily life (ADL) and QoL.[45,51,52] According to this clinical staging, *advanced stage* is the last stage in the clinical progression of PD, independently of what follows next until patients' death. But patients with MC do not necessarily manifest motor or NMS that are resistant to L-dopa, which is beautifully illustrated by PD patients selected to DBS who by definition have the most disabling MC and absence of such symptoms as psychosis, dementia, postural instability or falls.[81]

The use of the Hoehn and Yahr scale (HY scale) is an alternative way to define *advanced stage* PD.[42] In the pre-L-dopa era, Hoehn and Yahr[42] developed the staging system that bears their name to describe disease progression, combining in the scale the concepts of impairment (deficit in a body function or structure) and disability (the functional consequence of an impairment) **(Figure 1)**.[82] The scale was based on the concept that the severity of parkinsonism depended mainly on the presence of bilateral symptoms and compromise of gait and balance, and that physical independence was ultimately lost due to postural instability, gait disorder and severe bilateral parkinsonism.[42,82] The HY scale is still the most widely used tool to stage severity of parkinsonism.[83] Available data show that the HY scale, although anchored on motor signs, is able to capture other important features of PD: once patients reach stage 3 (loss of balance) there is a higher risk of dementia and decreased survival, and an increase in the scores of the Unified Parkinson`s Disease Rating Scale (UPDRS) despite drug adjustment.[82,84] On the other hand, it has been shown significant correlation between later HY stages and modern measures of motor impairment and worse scores in QoL.[85,86] *Advanced stage* PD is commonly defined as stages 4 and 5 of the HY scale, which corresponds with loss of physical independence.[82] This scoring is commonly performed during *off* periods, so that *advanced stage* PD is usually understood as patients in HY stage 4 or 5 during *off* period.

Nevertheless, some weaknesses of the HY scale can bias its use as a measure of disease progression. Incorporating two indices of severity, impairment and disability, can create

ambiguity and difficulty in classifying individual patients, as these indices do not necessarily progress in parallel and may even diverge.[82] These two indices are heavily weighted towards postural instability and lower limbs involvement, which increases the likelihood of not capturing disease progression due to other motor or non-motor symptoms.[82] Additionally, the HY scale is a categorical instrument, implying that an increment in stage does not necessarily mean a proportional overall increase in motor dysfunction, although in general a progression from stage 1 to 5 reflects global disease deterioration.[82] The option for 5 stages tends to collapse patients of different impairment severity in the same stage, creating clinical heterogeneity in each category of the scale.[82] Finally, as a pre-levodopa instrument, it does not capture MC. In spite of its limitations, the HY scale is widely used as a staging system of PD progression owing to the significant correlation of its later stages with the presence of symptoms poorly responsive to L-dopa, its worldwide acceptance and ease of use thus allowing for effortless replication of studies' results.

Advanced stage of Parkinson's disease: current definition and its limitations

As mentioned above, the classic concept of *advanced stage* PD is broad and depends upon the definition used. The most common criteria to define *advanced stage* PD is either the presence of MC or a stage 4 or 5 in the HY scale usually during *off* period,[42,45] although both can co-exist in a single patient. Depending on the definition used, *advanced stage* denotes different clinical features of PD, either the presence of MC or/and the presence of postural instability and physical dependence. In either definition, there is no later stage than *advanced stage*, independently of what happens to patients after they start MC or reach HY stage 4 or 5. However, the ELLDOPA trial[87] showed that MC may develop as soon as within 9 months of L-dopa treatment. Additional heterogeneity exists among *advanced stage* PD patients depending on the predominance and severity of non-motor and axial symptoms, and the severity of MC. The heterogeneity within the population of *advanced stage* patients was further incremented with the advent of DBS. This surgical technique radically changed the treatment of MC, as a powerful intervention to reduce the frequency and severity of MC and disability.[74] This motor improvement is maintained at least for 10 years with the exception of axial

symptoms and NMS, which gradually worsen 3-5 years after DBS.[76-78,88,89] For this reason, DBS has changed the natural history of *advanced stage* patients with MC, who no more manifest MC but will get further disability once L-dopa resistant symptoms emerge.

Evidence from clinical practice suggests that a sub-group of *advanced stage* PD patients will progress to a later stage of PD. Despite the severe disability in most advanced stages of PD, the clinical characteristics of late-stage PD (LS-PD) have been only partially described. This group of patients has very severe motor and non-motor symptoms which eventually respond poorly to dopaminergic therapy and for which we lack efficacious therapeutical interventions. These patients are dependent on others for ADL and tend to seek less often the Movement Disorders Units.

In our project, we defined LS-PD as patients in HY stage 4 or 5; to further guarantee that we would recruit very disabled patients, staging of patients was scored during *on* period, so that LS-PD describes PD patients in HY stage 4 or 5 during the best effect of L-dopa (*on* state).

Figure 1. Hoehn and Yahr staging

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 2.5 = Mild bilateral disease, with recovery on pull test.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.

AIMS OF THE STUDY

The present study aimed to characterize the later stages of PD. The purposes of the study were:

1. To describe the clinical features of PD patients in late-stage.
2. To determine the handicap and its contributing factors in late-stage PD.
3. To explore whether the handicap and its determinants in PD patients with disabling L-dopa-induced motor complications (advanced stage PD) differ from those of PD patients in late-stage.
4. To propose a definition of late-stage PD in the case these patients do represent a new distinct sub-group of advanced stage PD patients.
5. To review the therapeutic options for the treatment of NMS in late-stage PD.

CHAPTER 1: *Clinical features and medication use of Late-Stage PD*

Paper:

Late-stage Parkinson's disease: The Barcelona and Lisbon Cohort

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Late-Stage Parkinson's disease: The Barcelona and Lisbon Cohort

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ABSTRACT

Background: Studies of late stages of Parkinson`s disease (LS-PD) are limited. To provide an adequate health plan for patients in these most advanced stages, accurate information on their clinical condition is necessary.

Objective: Characterize clinical features and medication use of LS-PD.

Material & Methods: Cross-sectional study of LS-PD stage 4 or 5 of Hoehn & Yahr in *on*. Demographics, clinical features and medication data were obtained using a structured questionnaire and physical examination. Patients were asked to grade the perceived impact of symptoms on their health status.

Results: 50 patients (mean age 74.1 years and mean disease duration 17.9 years) were studied. Severe akinetic symmetric parkinsonism was present in most, with negligible rigidity and tremor, and most patients were wheelchair-bound. Severe postural instability and freezing of gait, causing frequent falls and fractures, and prominent dysarthria and dysphagia dominated the motor syndrome. Levodopa remained effective in most patients in relieving motor symptoms including tremor. Motor fluctuations and dyskinesias were present in 78% and 62% of patients respectively, but were not perceived as disabling. All had neuropsychiatric and dysautonomic symptoms. Visual hallucinations were present in 44%, depression in 62% and dementia in 50%. Lack of tremor ($p < 0.01$) and absence of depression ($p < 0.01$) were independently associated with dementia ($R^2 = 45\%$). Symptoms causing greatest impact on perceived health status were falls, gait unsteadiness, urinary dysfunction and sweats.

Conclusions: Motor and non-motor non-levodopa responsive problems were frequent and the main cause of disability. Fluctuations and dyskinesias were frequent though not disabling. Dementia is not unavoidable in these very late stages.

INTRODUCTION

Parkinson`s disease (PD) is a chronic disease with progressive disability. The clinical characteristics of late-stage PD (LS-PD), when disability is most severe, have been only partially described. In the pre-levodopa era, reporting on the clinical features of 100 parkinsonian patients, Martin *et al*[58] found that patients in later Hoehn and Yahr (H&Y) stages had frequent and severe cognitive decline besides severe motor impairment. In recent times, after the introduction of therapies such as levodopa or deep brain stimulation, cross-sectional studies have shown worsening of sleep problems, dysautonomia and cognition with advancing disease.[90,91] The longitudinal studies by Hely *et al,*[56-57] describe patients in late-stage PD with common but not disabling dyskinesias and on-off, with dementia and dependency on carers eventually occurring in most, whose major disability relates to motor and non-motor symptoms not improved by levodopa.

Better general healthcare, and better understanding of complications and clinical management of PD, is likely to increase the prevalence of LS-PD in the future.[92] These very advanced patients will represent an important burden for families and the healthcare system. Since knowledge of the health needs of these disabled patients is crucial to plan effective health resources that cover patients and caregivers needs, we thought to study the clinical features and handicap of LS-PD patients attending two tertiary centres, selected on the basis of motor disability. We report on this paper the results concerning the clinical features.

PATIENTS & METHODS

Study participants

PD patients who attend the movement disorders clinics of two tertiary university hospitals were studied. PD was diagnosed according to the UK Parkinson's Disease Society Brain Bank Criteria.[93] Patients in stage 4 or 5 of Hoehn and Yahr in *on* were included (stage 4 = patients with severe disability but still able to walk or stand unassisted; stage 5 = wheelchair bound or bedridden unless aided).[42] Patients with a diagnosis of parkinsonism other than idiopathic Parkinson`s disease were excluded. The study was approved by the local ethical committees. Informed consent was obtained from the patient or, if dementia was present, the caregiver.

Study design

This was a cross-sectional study performed in two tertiary university hospitals, one in Barcelona, Spain (Hospital Clínic Universitari) and other in Lisbon, Portugal (Hospital Santa Maria). Consecutive patients were recruited from the outpatient clinics during a 24 months period. Data were collected by interviewing patients or, if the patient was not competent, their caregivers. In those infrequent instances when only the caregiver was present in the outpatient clinic, the patient was later evaluated at home by one of the authors (MC).

Patients' evaluation

Data on demographics, clinical manifestations and disease management were obtained using a structured questionnaire and a physical examination form. Medical charts were reviewed when needed.

Severity of parkinsonism and activities of daily living (ADL) were evaluated using the Unified Parkinson`s Disease Rating Scale (UPDRS) and the Schwab & England Scale (S&E), respectively.[94,95] Part III (motor) of UPDRS was assessed during *on* period. Parkinsonism was considered asymmetric when right-left differences in tremor, bradykinesia and rigidity were ≥ 5 points on the UPDRS items 20-23 and 25-26.[96]

Levodopa-induced motor and non-motor complications were assessed with part IV of UPDRS, the structured questionnaire and the neurological examination. We established whether they were present at the time of evaluation, had been present in the past but

were currently absent, or had never been present. Patients were asked to rate current dyskinesias as either troublesome or not troublesome.

Non-motor symptoms were assessed in three domains: behavioural and cognition; dysautonomia; and other (sleep, fatigue, pain, paresthesias, anorexia, drooling and kyphoscoliosis).[97] Dementia and depression were diagnosed according to the DSM-IV definitions.[98] Cognition and mood were rated using the Mini Mental State Examination (MMSE) and The Beck Depression Inventory (BDI), respectively.[99,100] Orthostatic hypotension was defined as a decrease in systolic pressure ≥ 20 mmHg or / and in diastolic pressure ≥ 10 mmHg, within 3 minutes of standing. Patients were asked to grade the impact caused by symptoms on their perceived health status (0 = none; 4 = extreme).[97,101]

We obtained data on current medication use and side effects, and patients were asked to judge the response of symptoms to levodopa (improves; worsens; no response).

Statistical Analysis

The software program SPSS 12.0 (SPSS, Chicago, IL) was used for database and statistical analysis. We performed a descriptive analysis for each variable. Comparison of cohorts from Lisbon and Barcelona was done, using Independent Samples T Test and Mann-Whitney *U* Test for comparison of continuous variables, and Pearson Chi-square Test and Fisher Exact Test for differences in proportions. Concerning the impact caused by symptoms on patients` perceived health status, we calculated the median value (0 = none; 4 = extreme) for each symptom reported by patients. Variables associated with dementia (dependent variable) at a significance level of $p \leq 0.1$ were included in a multivariate logistic regression analysis, using likelihood ratio forward stepping. Two-tailed p values < 0.05 were considered significant.

RESULTS

Fifty patients were included (Barcelona 28, Lisbon 22). Demographic data are shown on **Table 1**. Disease characteristics were comparable in the two groups of patients, except for medication (see below).

Table 1 Demographic characteristics and Hoehn & Yahr stage score in late-stage PD patients

Characteristic	**PD patients**
n	50
Age (years) (mean (SD))	74.1 (7.0)
Women (n (%))	27 (54)
Age at disease onset (years) (mean (SD))	56.2 (10.4)
Duration of disease (years) (mean (SD))	17.94 (6.3)
Education (years) (mean (SD))	7.6 (4.7)
Hoehn & Yahr stage[a] (nº (%))	
4	30 (60)
5	20 (40)

Abbreviations: PD, Parkinson`s disease

[a] scored in *on* period.

Clinical Manifestations

Motor Symptoms

As expected, slowness of movement occurred in all patients, and was severe in most **(Table 2)**. Arm rest tremor was present in 8 (16%) (severe in 1), and also affected lower limbs in 2. Mild postural tremor was observed in 25 (50%) patients, including all the patients with rest tremor. Limb rigidity was detected in 32 patients (64%), and was mild in most. All patients had postural instability in accordance with selection criteria for the study.

Freezing of gait was reported by 31 patients (62%), and in 15 it was frequent and a cause of falls. Falls occurred in 25 (50%), and in 14 cases they occurred daily. Of those 25 patients, 20 were H&Y stage 4 and 5 were H&Y stage 5. Forty-eight (96%) reported problems with speech, which was difficult to understand or unintelligible in 26. Dysphagia was reported by 34 (68%). Ten experienced occasional choking, thirteen required soft food, seven had a nasogastric tube, and in five feeding was through a gastrostomy.

At the time of evaluation, 72% of patients perceived that levodopa improved mobility, and 90% that it improved tremor. 73% of patients thought levodopa had no effect on unsteadiness, and 16% had the perception levodopa worsened falls. Still, 52% thought it improved freezing. Though 37% of patients reported some benefit from levodopa on speech, dysphagia did not improve among 82%.

Table 2 Motor symptoms in late-stage PD patients

	PD patients (n = 50)
Asymmetric disease (n (%))	16 (32)
Slowness of movement (n (%))	50 (100)
UPDRS limb bradykinesia items, median[a]	3
Postural instability (n (%))	50 (100)
Dysarthria (n (%))	48 (96)
UPDRS speech, median[a]	3
Neck rigidity (n (%))	39 (78)
UPDRS neck rigidity, median[a]	2
Dysphagia (n (%))	34 (68)
UPDRS swallowing, median[a]	2
Limb rigidity (n (%))	32 (64)
UPDRS limb rigidity items, median[a]	1
Freezing (n (%))	31 (62)
Falls (n (%))	25 (50)
Tremor (n (%))	25 (50)
Rest tremor (n (%))	8 (16)
Asymmetric rest tremor (n (%))	7 (14)
Postural tremor (n (%))	25 (50)
Head tremor (n (%))	2 (4)
UPDRS tremor items, median[a]	0
Fixed dystonia (n (%))	24 (48)
Bone fractures in the previous 5 years (n (%))	10 (20)
Need for a wheelchair (n (%))	39 (78)
Gastrostomy (n (%))	5 (10)
UPDRS motor *on* (mean (SD))[a]	49.18 (13.0)

Abbreviations: UPDRS, Unified Parkinson`s Disease Rating Scale; PD, Parkinson`s disease.

[a] Higher numbers indicate a greater severity of impairment.

Levodopa-induced motor complications

Levodopa-induced motor complications were present in 39 patients (78%) at the time of the study (motor fluctuations in 39; dyskinesias in 31) **(Table 3)**. They had occurred in an additional eight patients (motor fluctuations in 8; dyskinesias in 2) at some point during the disease course but had later remitted. Wearing-off occurred in all 39 patients. O*ffs* occupied < 25% of the day in 19, 26-50% of the day in 8, and > 75% of the day in 7 patients. The mean difference in UPDRS ADL score (n=39) between *on* and *off* was statistical significant ($p < 0.05$), and the same was found for the Schwab & England Scale (n=39) ($p < 0.01$) **(Table 4)**.

Dyskinesias were troublesome in 13 (26%), but in only 4 they were severely disabling (UPDRS score 3 or 4). Dyskinesias occupied < 25% of the day in 17, and > 75% of the day in 4 patients.

Table 3 Levodopa-induced complications in late-stage PD patients at the time of study assessment

	PD patients (n = 50)
L-dopa-induced motor complications (n (%))	39 (78)
Wearing-off (n (%))	39 (78)
Off duration > 75% of the day (n (%))	7 (14)
No *on* response (n (%))	17 (34)
Morning dystonia (n (%))	11 (22)
Off dystonia (n (%))	9 (18)
Delayed *on* response (n (%))	7 (14)
Morning akinesia (n (%))	5 (10)
On/off phenomena (n (%))	2 (4)
Dyskinesia (n (%))	31 (62)
peak-dose (n (%))	15 (30)
diphasic (n (%))	9 (18)
square-wave (n (%))	7 (14)
Troublesome dyskinesias (n (%))	13 (26)
Dyskinesia duration > 75% of the day (n (%))	4 (8)
Severe or complete disabling dyskinesia (n (%))	4 (8)
L-dopa-induced non-motor fluctuations (n (%))	33 (66)
Neuropsychiatric (n (%))	24 (48)
Disautonomic (n (%))	11 (22)
Sensory (n (%))	8 (16)
UPDRS part IV (mean (SD))[a]	5.3 (3.5)

Abbreviations: UPDRS part IV, treatment complications component of Unified Parkinson`s Disease Rating Scale; PD, Parkinson`s disease; L-dopa, levodopa.

[a] Higher numbers indicate a greater severity of impairment.

Table 4 Performance in the activities of daily living of Late-Stage PD patients.

Activities of daily living		
UPDRS ADL (mean (SD))[a]		
on	28.2 (6.3)	$p < 0.05$[c]
off	29.6 (5.8)	
S&E (mean (SD))[b]		
on	31.0 (15.7)	
off	23.2 (14.2)	$p < 0.01$[c]

Abbreviations: UPDRS, Unified Parkinson`s Disease Rating Scale; ADL, activities of daily living; S&E, Schwab and England scale;

[a] Higher numbers indicate a greater impairment.

[b] Higher numbers indicate more independency in the activities of daily living.

[c] Not considered clinical relevant

Cognition, Mood and Behaviour

Neuropsychiatric symptoms were present at the time of examination in all patients **(Table 5)**. Visual hallucinations and delusions had occurred in an additional 22 and 9 patients, respectively, at some point during the disease course but had later remitted.

Thirty-one patients (62%) were depressed. Nineteen depressed patients also reported symptoms suggestive of apathy.

Dementia was present in 25 (50%) patients. Mean MMSE score in 22 demented patients was 11.8 (SD ± 6.5), while it was 23.5 (SD ± 4.5) in the non-demented. The MMSE cut-off score is adjusted to literacy in Spain and Portugal and the above value of 23.5 points does not configure dementia in those populations. Thirteen demented patients reported visual hallucinations and 10 delusions. Variables (univariable analysis) that were statistically significantly associated with the presence of dementia were lack of tremor ($p < 0.01$), absence of depression ($p < 0.01$), symptoms suggestive of apathy ($p < 0.01$), daytime somnolence ($p < 0.05$), absence of irritability ($p < 0.05$), less consumption of antiparkinsonian drugs ($p < 0.01$), and worse scores on UPDRS ADL part ($p < 0.01$), UPDRS part IV ($p < 0.05$) and S&E scale ($p < 0.05$). In a multivariable logistic regression analysis,

lack of tremor ($p < 0.01$) and absence of depression ($p < 0.01$) remained independently associated with dementia. This model could predict the presence of dementia in 72% of the cases and explained its occurrence in 45% (Nagelkerke R Square).

Neuropsychiatric symptoms severity changed with levodopa intake in 48% of patients **(Table 3)**. Improvement after a levodopa dose was reported in sadness (13.5% of patients), apathy (32%), slowness of thinking (44%), anxiety (25%), and irritability (37%). Worsening of anxiety and irritability was reported by a small proportion of patients (8% and 5%, respectively). Aggressive behaviour was mostly (75%) unaffected by levodopa.

Dysautonomic complications

Dysautonomic symptoms occurred in 48 patients (96%) **(Table 5)**. We measured arterial blood pressure in 18 and documented orthostatic hypotension in 3.

Pain, sleep and other symptoms

Sleep disturbances were very frequent and sensory symptoms were reported by 19 patients (38%) **(Table 5)**.

Table 5 Non-motor complications in late-stage PD patients

	PD patients (n = 50)
Cognition, Mood & Behaviour (n (%))	50 (100)
Depression (n (%))	31 (62)
BDI in 15 testable depressed patients (mean (SD))	16.8 (5.29)
Symptoms suggestive of apathy (n (%))	28 (56)
Slowness of thinking (n (%))	25 (50)
Anxiety (n (%))	25 (50)
Dementia (n (%))	25 (50)
MMSE in 44 testable patients (demented and non-demented) (mean (SD))	17.7 (8.1)
MMSE in 22 demented patients (mean (SD))	11.8 (6.5)
MMSE in 22 non demented patients (mean (SD))	23.5 (4.5)
Visual hallucinations (n (%))	22 (44)
Irritability (n (%))	20 (40)
Delusions (n (%))	16 (32)
Aggressive behaviour (n (%))	8 (16)
UPDRS part I (mean (SD))[a]	6.4 (3.9)
Dysautonomic complications (n (%))	48 (96)
Constipation (n (%))	41 (82)
Urinary dysfunction ((incontinence, urgency or retention) (n (%))	32 (64)
Hyperhidrosis (n (%))	18 (36)
Sweats (n (%))	18 (36)
Orthostatism (item 42 of UPDRS) (n (%))	13 (26)
Dyspnea (n (%))	7 (14)
Syncope (n (%))	4 (8)
Pain, Sleep & other symptoms	-
Night sleep problems (n (%))	30 (60)
Diurnal somnolence (n (%))	18 (36)
Pain (n (%))	12 (24)
Anorexia (n (%))	11 (22)
Paresthesias (n (%))	10 (20)
Sleep attacks (n (%))	5 (10)
Weight loss (n (%))	7 (14)
Fatigue (n (%))	18 (36)
Drooling (n (%))	35 (70)
Kyphoscoliosis (n (%))	8 (16)

Abbreviations: MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory; UPDRS, Unified Parkinson`s Disease Rating Scale; PD, Parkinson`s disease.[a] Higher numbers indicate a greater severity of impairment.

Impact of symptoms on perceived health status

Symptoms causing an extreme or severe impact on patients` perceived health status were in most instances motor and non-motor symptoms that do not respond to levodopa **(Table 6)**.

Table 6 Symptoms causing an extreme or severe impact on patients` perceived health status in Late-Stage PD patients.

Impact of symptoms on patients` perceived health status		
Symptoms with extreme impact (score 4)	falls unsteadiness	urinary dysfunction sweats
Symptoms with severe impact (score 3)	bradykinesia freezing speech problems dysphagia	apathy anxiety depression dementia constipation dyspnea pain

Medication

At the time of the study, 49 patients (98%) were taking levodopa, as monotherapy (n = 18) or in combination with other antiparkinsonian drugs (n = 31) **(Table 7)**. Mean daily doses of ropinirole was 6 ± 3.6 mg/d; of pergolide 1.8 ± 1.2 mg/d; of pramipexole 0.68 ± 0.42 mg/d; of cabergoline 2.5 ± 2.4 mg/d; of bromocriptine 10.7 ± 5.1 mg/d and of piribedil 150 ± 0.0 mg/d. Statistical significant differences between the Lisbon and Barcelona cohorts were found in the frequency of patients on bromocriptine (Lisbon= 6 vs Barcelona= 1 patients; p = 0.04) and in the mean daily dose of levodopa (Lisbon= 934 ± 352.5 mg *vs* Barcelona= 688 ± 234.4 mg; p = 0.01). The mean daily dose of levodopa did not differ significantly between patients with and without motor complications. Twenty-five patients (50%) were taking atypical neuroleptics because of delusions and visual hallucinations. Fifteen of them were demented. Clozapine was the most frequently prescribed neuroleptic (n = 19), at a mean daily dose of 56.5 ± 71.0 mg/d, while

quetiapine was prescribed in 5 patients (mean daily dose 125 ± 90.1 mg/d). Fourteen patients (28%) were on antidepressants, while nearly half were on benzodiazepines: 56% because of anxiety and 50% because of nocturnal sleep disturbances.

Table 7 Medication in late-stage PD patients

	PD patients (n = 50)
Levodopa (n (%))	
total	49 (98)
monotherapy	18 (36)
in combination	31 (62)
Daily dose of levodopa (mg) (mean (SD))	785 (318)
Range of daily dose of levodopa (mg)	250-1900
Agonists (n (%))	25 (50)
Amantadine (n (%))	9 (18)
Entacapone (n (%))	6 (12)
Selegiline (n (%))	5 (10)
Anticholinergics (n (%))	1 (2)
Brain surgery for PD (n (%))	4 (8)
Neuroleptics (n (%))	25 (50)
Benzodiazepines (n (%))	22 (44)
Antidepressants (n (%))	14 (28)
Rivastigmine (n (%))	2 (4)
Non neurological medication (n (%))	32 (64)

Abbreviations: PD, Parkinson`s disease

DISCUSSION

As expected, we have found that this cohort of LS-PD had long-standing disease, with severe motor and frequent and severe non-motor symptoms. Levodopa-induced motor complications were frequent but generally not disabling. Symptoms causing the highest disability, such as falls, postural instability and many non-motor symptoms, were non-levodopa responsive. Medication was mainly targeted at improving motor symptoms, and, in two-thirds of patients, consisted of levodopa associated with other antiparkinsonian drugs. Dosage of these drugs was probably influenced by the frequent occurrence of neuropsychiatric symptoms, such as psychosis. Although patients reported some benefit from levodopa, this was of limited clinical relevance. The scores in UPDRS-ADL and S&E in *on* and *off*, although statistical significant, showed that patients were highly disabled and dependent on caregivers in either levodopa state. Other treatments were directed to the correction of psychosis, anxiety, sleep disturbances and depression.

Our data do give some insight about the clinical characteristics of LS-PD and may have implications on how we manage their illness. Information on clinical features of LS-PD is relatively sparse.[42,56-59,90] Papapetropoulos and Mash[59] have reported on the frequency of motor complications on a cohort of 61 patients with LS-PD, although only two thirds of their patients were H&Y greater than 3. Recently, The Sydney Multicenter Study reported on the 30 patients surviving after 20 years of follow-up, most in H&Y stage 4.[57] These patients were initially recruited into a clinical trial, which may have influenced entrance characteristics and subsequent management.

The cohort

We selected patients based on motor PD severity, and not disease duration. The mean disease duration (18 years) was longer than previously reported in other studies that included severely disabled patients.[56,69,102] However, age at disease onset was similar, excluding early disease onset as the cause of prolonged survival.[56,58,102] We included more females than males. This excess of women might be related to shorter life expectancy of men compared to women.

Patients` perceived health status and ADL

The symptoms most contributing to diminished perceived health status, in line with other reports, were mostly non-levodopa responsive, and for the majority we lack efficacious therapeutic interventions.[56,57] And even for the ones where treatment is available, such as depression and anxiety, about half were not prescribed any treatment, suggesting that clinicians may have under-recognized or underestimate these symptoms.

Motor symptoms

Most patients had symmetric disease, possibly a sign of PD progression.[96] Bradykinesia had a profound impact on patients` disability, while rigidity was generally mild and rest tremor was uncommon. Falls and related fractures (20%) were common but perhaps lower than expected, probably since the majority of patients (78%) were wheelchair-bound. Our findings are in line with those of a recent meta-analysis, that found a 3-month fall rate of 46% and that falls decreased in later stages of disease.[103] Dysarthria had a great impact on patients` condition, interfering with communication with caregivers, whereas dysphagia was a frequent cause of choking and tube feeding. Pneumonia, frequently caused by aspiration, was the most common cause of death in the Sydney cohort, suggesting that an aggressive intervention on dysphagia might prolong survival.[56,57,104]

Levodopa-induced motor complications

Overall, levodopa-induced motor complications occurred frequently in our cohort (78%), findings similar to those from Papapetropoulos and Mash[59] (88.5%) and from the Sydney studies (95%).[56,57] In our cohort, *offs* were characterised by high disability and dependency on caregivers, although they were of short duration. Even so, patients did not value the relative impact of *offs* compared to *ons*, probably because they also were doing poorly in the *on* state. Dyskinesias were frequent, but troublesome in only a minority, and patients were free of dyskinesias for most of the day. Likewise, in the study of Papapetropoulos and Mash,[59] dyskinesias (60.6%) were severe in only 6 cases. The Sydney studies also reported not disabling levodopa-induced motor complications.[56,57] They occurred in most at either 15 and 20 years, but severe dyskinesias only afflicted 10% of patients, and in just 17% an *off* > 75% of the day was reported.[56,57]

LS-PD cohorts with a high frequency of motor fluctuations, as ours, may represent a subset of LS-PD with long survival. When comparing moderate-severe motor fluctuators with non-fluctuators, Kempster *et al*[105] found that the development of disease milestones (falls, hallucinations, cognitive disability and institutionalization) was determined solely by age, not disease duration or presence of fluctuations. Fluctuators had a significantly longer disease duration when they reached milestones.[105] Our cohort reinforces that patients with fluctuations reach milestones as do patients without fluctuations.

Non-motor complications of PD

Non-motor symptoms, mostly neuropsychiatric and dysautonomic, were prominent in our cohort. The number of patients with neuropsychiatric symptoms was higher than the one reported by Aarsland *et al*[60] (61%), where only a 23% of patients were in a Hoehn & Yahr stage of 4, suggesting that more advanced disease is associated with a higher frequency of neuropsychiatric symptoms. However, the type and relative frequency of symptoms were similar, indicating that the presence of most symptoms is independent of staging.[60,106]

Our figure (62%) for depression is similar to that found in the Sydney studies,[56,57] but higher than the 43% reported by Papapetropoulos *et al*,[90] in a retrospective study. Possibly, the prominent dysarthria, cognitive impairment, severe hypomimia and apathy might have biased this figure.[107]

Almost half (44%) had visual hallucinations at the time of study assessment, consistent with the late stage of their illness.[56,57,90,91,108,109] The presence of hallucinations probably explains the low doses of agonists, and frequent use of levodopa as monotherapy. Hallucinations were a major cause of morbidity, as 55% of those with hallucinations rated them as causing an extreme or severe impact on their perceived health status. This severe disability is also indirectly expressed in the widespread use of neuroleptics (50%).

Only 50% of the patients were diagnosed with dementia, percentage lower than in other series that claim inevitability.[57] Diagnosis of dementia was based on clinical examination and not on neuropsychological assessment, and this might explain the differences reported. Our frequency is similar to that found in the Sydney study[56] at 15 years (48%), by Papapetropoulos *et al*[90] (50.7%), and by Kempster *et al*[105] (55.6%). It differs from that in the Sydney cohort at 20 years[57] (83%), but in this study the duration of PD was longer,

even though the mean age of patients was similar to ours. Besides that, in the Sydney cohort 26 patients were already demented at baseline neuropsychological assessment.[57] It also differs from the one found by Aarsland *et al*[61] after 8 years of follow-up (78%). However, these authors[61] calculated the period prevalence and not point prevalence, combining prevalence, incidence and mortality rates. Importantly, the data from Hely *et al*[57] and Aarsland *et al*[61] are longitudinal which increments its reliability compared to our cross-sectional data collection.

Lack of tremor and absence of depression independently predicted the presence of dementia. Published data has shown better prognosis and preserved cognition in tremor-predominant PD.[110,111] Depression has been found to correlate variably with cognitive decline.[56,112-114] We may assume that demented patients are less likely to report or show depression, and that could be an explanation to our findings. As some studies suggest that depression associates with cognitive decline, longitudinal data are essential to disclose how depression and dementia relate to each other at different stages of cognitive function.

Forty-eight patients (96%) had symptoms suggestive of autonomic dysfunction. In a quarter, orthostatism was symptomatic, but syncope was rare, and none was under specific treatment. Prominent urinary dysfunction and constipation, as well as sweats, were very common, and responsible for severe disability. Night sleep problems were not significantly troublesome, contrary to common belief. Pain was uncommon but very disabling, unlike results of two cross-sectional studies that reported higher pain frequencies (62-70%), even though in patients less advanced than ours`.[115,116]

Medication

Nearly all patients took levodopa either on monotherapy or in association with other antiparkinsonian drugs, mainly dopamine agonists at low doses. The mean dose of levodopa was in the same range of that in the Sydney cohort[56,57] and in the study by Papapetropoulos and Mash[59], but much lower than the mean dose of advanced PD patients that are candidates to deep brain stimulation (about 1100 mg).[74,117] Overall, patients still reported some benefit from levodopa intake, namely in motor slowness and tremor. Patients with motor fluctuations had however "poor" *ons*, with a change in disability between *on* and *off* that was of little clinical relevance. Similar to reported by

others, a small portion of our patients had a remission of motor fluctuations.[59] Although we can not ruled out that changes in doses or pattern of the dopaminergics treatment can be responsible for such remission, this finding could be also explained by increasing extranigral pathology along with the disease progression.[1,118]

Shortcomings

We studied a convenience sample of hospital-based patients, who were under the care of our tertiary clinics. Our recruitment rate was low (25 patients per year per centre), which strongly suggests that patients withdraw from specialized medical care once they reach an advanced stage. Our results, then, may not be representative for the entire population of LS-PD, namely, we cannot draw any firm conclusion regarding the prevalence of dementia in these late stages of the disease. Additionally, recruiting patients from two countries could have led to a heterogeneous sample. Nonetheless, except in the use of antiparkinsonian drugs, which most likely reflects different prescription practices, the sample was rather homogeneous.

Conclusions

In this hospital-based cohort of LS-PD patients, both motor and non-motor non-levodopa responsive problems were the main cause of disability. Half of the patients were considered non-demented, questioning the inevitability of dementia at late-stage. Levodopa-induced motor complications were frequent though not generally disabling, possibly since swings between *on* and *off* were of small magnitude. Future interventions, either pharmacological or non-pharmacological, and research and allocation of funds must focus on non-levodopa responsive aspects of the disease.

CHAPTER 2: *Handicap in Late-Stage PD*

Paper:

Dementia and severity of parkinsonism determines the handicap of patients in late-stage Parkinson's disease: The Barcelona-Lisbon Cohort

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Dementia and severity of parkinsonism determines the handicap of patients in late-stage Parkinson's disease: The Barcelona-Lisbon Cohort

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Keywords: Parkinson`s disease; late stage; advanced; dementia; disability; handicap; quality of life, caregiver

ABSTRACT

Background: Handicap has not been explored as a patient-centred outcome measure in Parkinson's disease (PD). The clinical features and medication use in late stages of PD (LS-PD) were reported previously. **Material & Methods:** Handicap, medical conditions, use of healthcare resources and the impact of LS-PD upon caregivers were characterized in a cross-sectional study of LS-PD stages 4 or 5 of Hoehn and Yahr (H&Y). Handicap was measured using the London Handicap Scale (LHS; 0=maximal handicap; 1=no handicap). **Results:** The mean LHS score in 50 patients was 0.33 (SD±0.15). The presence of dementia, the UPDRS part I score and H&Y stage in *off* independently predicted the LHS score (adjusted R^2=0.62; p=0.000). Co-morbidities and past medical conditions were frequent. Thirty-five patients lived at their house. Forty-five received unpaid care. Mean visits to family doctor in preceding 6 months were 2.2 (SD±3.0) and to neurologist 1.7 (SD±1.0). Use of other health resources was low. Unpaid caregivers spent much time with patients and reported a high burden. **Conclusion:** Handicap could be measured in LS-PD and LHS was easily completed by patients and caregivers. The high handicap in our cohort was mostly driven by the presence of dementia, behavioural complaints and the severity of non-dopaminergic motor features. Patients visited doctors infrequently and made low use of health resources, while unpaid caregivers reported a high burden.

INTRODUCTION

There are few published studies on late-stage Parkinson's disease (LS-PD).[57,58] A hospital-based population of LS-PD has recently been reported by us.[119] These subjects were severely disabled mostly from non-levodopa responsive problems, and suffered frequent motor fluctuations and dyskinesias.

The impact that PD has on patients has been addressed using several outcome measures, such as disability, interference in activities of daily living (ADL) or quality of life (QoL).[101,123,124] Handicap, an outcome measure widely used in chronic neurological or non-neurological diseases,[125,126] has never been used in PD. The World Health Organization (WHO) defines handicap as "(…) a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal, depending on age, sex, and social and cultural factors, for that individual",[127] and thus it is central to the management of patients with chronic diseases.[128] Handicap seems a more understandable concept to patients than QoL and a more meaningful measure of the impact of disease in the health status (HS) of an individual patient. The London Handicap Scale (LHS) is one of the most frequently used instruments to measure handicap[126,129,130] but has never previously been used in PD. It has proven good validity, reliability, sensitivity to change and transcultural validation.[129-132]

The results concerning handicap caused by very advanced PD are reported. In addition, the presence of co-morbidities and past medical conditions, health resources use and the impact of disease on caregivers are described.

PATIENTS & METHODS

Objectives:

Primary: quantify the handicap of a hospital-based population of LS-PD patients and to identify its determinants. *Secondary*: determine co-morbidities and past medical conditions; quantify the use of health resources; assess the impact of disease upon the caregivers.

Study participants

PD patients attending the movement disorders outpatient clinics of two university hospitals, one in Barcelona, Spain (Hospital Clínic Universitari) and other in Lisbon, Portugal (Hospital Santa Maria). PD was diagnosed according to the UK Parkinson's Disease Society Brain Bank Criteria.[93] Patients in stage 4 or 5 of Hoehn and Yahr (H&Y) in *on* were included (stage 4 = patients with severe disability but still able to walk or stand unassisted; stage 5 = wheelchair bound or bedridden unless aided).[42] Patients' informal caregivers (unpaid caregivers) were interviewed. The study was approved by the local ethical committees and written informed consent was obtained.

Study design

A cross-sectional study in subjects consecutively recruited during a 24-months period.

Participants' evaluation

Patients

Data on demographics, clinical manifestations and disease management, co-morbidities and past medical conditions, and usage of healthcare resources were obtained using a structured questionnaire (interviewing the patients and caregivers), a physical examination form and review of medical charts when needed. Details of other assessments performed in this same group of patients have been reported previously.[119] Briefly, patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Schwab & England Scale (S&E)[94]; a structured questionnaire adapted from Witjas *et al*[97] to assess non-motor symptoms in three domains: behavioural and cognition; dysautonomia; and other (sleep, fatigue, pain, paresthesias, anorexia, and drooling); dementia and depression were diagnosed according to the DSM-IV definitions[98]

and rated using the Mini Mental State Examination[99] and The Beck Depression Inventory,[100] respectively.

Handicap was assessed using the LHS.[129,130] This scale was developed to determine the effect of chronic disease on a person's functional ability.[126,129-132] It takes around 10 minutes to be completed, and consists of a self-completed questionnaire, though the descriptions of questions are objective enough for completion by a proxy. The questionnaire has 6 questions, one for each domain of handicap (mobility, physical independence, occupation, social integration, orientation, and economic self sufficiency) and each question contains six sentences hierarchically describing the degree of handicap; for each question, the patient must choose the most suitable sentence. Each sentence is assigned a scale weight. The questionnaire comprises a matrix of scale weights which when combined give a total score for handicap, to which a constant value of 0.456 is added; the final score ranges from 0 (maximal handicap) to 1 (no handicap).

Caregivers

Informal caregivers were asked to rate the impact of PD on their life (0 = no impact; 4 = maximal impact)[97] and the time per week they spent caregiving. The time allocated to caregiving was calculated by multiplying number of hours per day x number of days per week.

Statistical Analysis

The software program SPSS 14.0 (SPSS, Chicago, IL) was used. We performed a descriptive analysis of demographic data, of motor symptoms according to UPDRS and structured questionnaire and NMS according to structured questionnaire adapted from Witjas *et al,*[97] of the impact of symptoms on perceived HS (impact on perceived HS rated by patients, 0 = no impact; 4 = extreme impact),[119] of medication use, of associated medical conditions, of patients' residency ("own home", "relatives' home" or "nursing home") and use of health resources, and of caregiver burden according to time allocated to caregiving and the impact of PD on caregivers' life. A descriptive analysis of the LHS total score and sub-scores was performed.

Comparison of cohorts from Lisbon and Barcelona was done. Independent Samples T Test and Mann-Whitney *U* Test were used for comparison of continuous variables, and Pearson Chi-square Test and Fisher Exact Test for differences in proportions. Univariable

analysis was performed, and variables associated with the LHS score at a significance level of $p \leq 0.1$ were entered in a multiple linear regression analysis using the LHS total score as dependent variable. Two-tailed *p* values < 0.05 were considered significant.

RESULTS

Patients

Fifty patients were studied. Results on demographics, clinical manifestations and medication use have been reported previously[119] and shown in **Tables 1** and **2**.

Table 1 Demographics and medication use in late-stage PD patients

Characteristic	**PD patients (N = 50)**
Female (n (%))	27 (54)
Patients from Barcelona (n (%))	28 (56)
Patients from Lisbon (n (%))	22 (44)
Age (years) (mean (SD))	74.1 (7.0)
Duration of disease (years) (mean (SD))	17.94 (6.3)
Hoehn & Yahr stage[a] (nº (%))	
4	30 (60)
5	20 (40)
Levodopa (n (%))	49 (98)
monotherapy	18 (36)
in combination	31 (62)
Daily dose of levodopa (mg) (mean (SD))	785 (318)
Range of daily dose of levodopa (mg)	250-1900
Agonists (n (%))	25 (50)
Amantadine (n (%))	9 (18)
Entacapone (n (%))	6 (12)
Selegiline (n (%))	5 (10)
Anticholinergics (n (%))	1 (2)
Brain surgery for PD (n (%))	4 (8)
Neuroleptics (n (%))	25 (50)
clozapine (n (%)); daily dose (mg) (mean (SD))	19 (38); 56.5 (71.0)
quetiapine (n (%)); daily dose (mg) (mean (SD))	5 (10); 125 (90.1)
other (n (%))	1 (2)
Benzodiazepines (n (%))	22 (44)
Antidepressants (n (%))	14 (28)
Rivastigmine (n (%))	2 (4)
Non neurological medication (n (%))	32 (64)

Abbreviations: PD, Parkinson's disease; [a] Scored during on period

Table 2 Clinical manifestations in late-stage PD patients

Clinical manifestation	**PD patients (N = 50)**
UPDRS motor *on* (mean (SD))[b]	49.18 (13.0)
UPDRS ADL (mean (SD))[b]	
on	28.2 (6.3)
off	29.6 (5.8)
S&E (mean (SD))[c]	
on	31.0 (15.7)
off	23.2 (14.2)
Asymmetric disease (n (%))	16 (32)
UPDRS limb bradykinesia items, median[b]	3
Limb rigidity (n (%))	32 (64)
Rest tremor (n (%))	8 (16)
Postural tremor (n (%))	25 (50)
Postural instability (n (%))	50 (100)
Freezing (n (%))	31 (62)
Falls (n (%))	25 (50)
UPDRS speech, median[b]	3
UPDRS swallowing, median[b]	2
L-dopa-induced motor complications (n (%))	39 (78)
Wearing-off (n (%))	39 (78)
off duration > 75% of the day (n (%))	7 (14)
Dyskinesia (n (%))	31 (62)
Troublesome dyskinesias (n (%))	13 (26)
L-dopa-induced non-motor fluctuations (n (%))	33 (66)
Cognition, mood and behavior (n (%))	50 (100)
Visual hallucinations (n (%))	22 (44)
Delusion (n (%))	16 (32)
Dementia (DSM-IV) (n (%))	25 (50)
MMSE (mean (SD))	17.7 (8.1)
Anxiety (n (%))	25 (50)
Irritability (n (%))	20 (40)
Aggressive behavior (n (%))	8 (16)
Depression (DSM-IV) (n (%))	31 (62)
BDI (mean (SD))	16.8 (5.29)
Symptoms suggestive of apathy (n (%))	28 (56)

UPDRS part I (mean (SD))[b]	6.4 (3.9)
Dysautonomic complications (n (%))	48 (96)
Orthostatic hypotension[d] (n (%))	3 (6)
Orthostatism (item 42 of UPDRS) (n (%))	13 (26)
Syncope (n (%))	4 (8)
Constipation (n (%))	41 (82)
Urinary dysfunction (incontinence, urgency or retention) (n (%))	32 (64)
Hyperhidrosis (n (%))	18 (36)
Sweats (n (%))	18 (36)
Dyspnea (n (%))	7 (14)
Night sleep problems (n (%))	30 (60)
Diurnal somnolence (n (%))	18 (36)
Pain (n (%))	12 (24)
Drooling (n (%))	35 (70)

Abbreviations: PD, Parkinson's disease; UPDRS, Unified Parkinson's disease Rating Scale; ADL, activities of daily living; S&E, Schwab and England scale. [a] Scored during on period; [b] Higher numbers indicate a greater severity of impairment; [c] Higher numbers indicate more independency in the activities of daily living; [d] We were able to measure arterial blood pressure in 18 patients; MMSE, Mini Mental State Examination; BDI, Beck Depression Inventory

Handicap

LHS values followed a Gaussian distribution with a mean LHS total score of 0.338 (SD ± 0.155) **(Table 3)**. The most affected domain was Orientation.

In simple linear regression analysis, the following variables were significantly correlated with the total LHS score: dementia (DSM-IV) ($p < 0.001$); depression (DSM-IV) ($p < 0.05$); unsteadiness causing severe or extreme impact on patients' perceived HS ($p < 0.05$); falls causing severe or extreme impact on patients' perceived HS ($p < 0.05$); hallucinations ($p < 0.05$); H&Y in *on* ($p < 0.01$); H&Y in *off* ($p < 0.005$); patients' residency ($p < 0.05$); UPDRS part I score ($p < 0.01$); UPDRS part II score in *on* ($p < 0.01$) and *off* ($p < 0.05$); S&E score in *on* ($p < 0.001$) and *off* ($p < 0.01$); and wearing-off ($p < 0.05$). Dementia (DSM-IV) was not correlated with UPDRS part I.

In multiple linear regression analysis using backwards method, the independent variables that still remained significant were dementia (DSM-IV), UPDRS part I score, H&Y stage in *off*, S&E score in *on*, wearing-off and falls. The variables that best predicted the total

score of LHS in the final model were presence of dementia (DSM-IV) (r = - 0.66; $p < 0.000$), UPDRS part I score (r = - 0.57; $p < 0.000$) and H&Y stage in *off* (r = - 0.47; $p = 0.001$) **(Table 4)**. This model explained 62% of the variance in the total score of LHS ($p = 0.000$). The Durbin-Watson test and collinearity statistics showed lack of correlation and multicollinearity between the independent variables.

Table 3. Total and sub-scores in the 6 domains of London Handicap Scale in Late-Stage PD patients

	Total	**Mobility**	**Physical independence**	**Occupation**	**Social integration**	**Orientation**	**Economic self-sufficiency**
Mean (SD)	0.338 (0.155)	-0.042 (0.044)	-0.057 (0.003)	-0.047 (0,051)	0.007 (0,031)	0.004 (0.074)	0.013 (0.062)
Median	0.325	-0.036	-0.057	-0.035	0.007	-0.008	0.033
Minimum / maximum	0.044 / 0.628	-0.108 / 0.038	-0.061 / - 0.053	-0.350 / 0.099	-0.041 / 0.063	-0.075 / 0.109	-0.111 / 0.100
Minimum / maximum possible values for total score [a] and each domain sub-score [b]	0 / 1	-0.108 / 0.071	-0.061 / 0.102	-0.060 / 0.099	-0.041 / 0.063	-0.075 / 0.109	-0.111 / 0.100

Abbreviations: PD, Parkinson's disease; SD, standard deviation; [a] In the London Handicap Scale total score, 0 indicates total disability and 1 indicates normal function; [b] In the London Handicap Scale sub-scores of the 6 domains, the minimum value indicates most severe disadvantage and the maximum value indicates no disadvantage.

Table 4. Multiple linear regression model for London Handicap Scale

Independent variables	**Unstandardized Beta**	**Standardized Beta**	**SE**	**95% CI**	***P***	**Dependent variable**	**R**	**R^2**	**Adjusted R^2**	***P***
Presence of dementia (DSM-IV)	- 0.125	- 0.408	0.037	- 0.200; - 0.051	0.02	Total score in London Handicap Scale	0.8	0.65	0.62	0.000
Score in UPDRS Part I	- 0.015	- 0.368	0.005	- 0.024; - 0.005	0.03					
Hoehn & Yahr staging in *off*	- 0.115	- 0.361	0.034	- 0.183; - 0.046	0.02					

Abbreviations: PD, Parkinson's disease; UPDRS, Unified Parkinson's disease Rating Scale; SE, standard error

Co-morbidities and past medical conditions

Thirty-seven patients (74%) had co-morbidities while 27 (54%) reported past medical conditions **(Table 5)**. We found no significant differences in the mean total score of LHS between patients with and without past or concomitant medical diseases, or those with > 2 past or concomitant medical diseases.

Table 5. Co-morbidities and past medical conditions in late-stage PD patients

	PD patients (n = 50)
Co-morbidities (n (%))	37 (74)
Musculoskeletal diseases (n (%))	20 (40)
Cardiovascular disease (n (%))	14 (28)
Benign prostate hypertrophy (n (%))	8 (16)
Eye cataract (n (%))	7 (14)
Weight loss (n (%))	7 (14)
Skin infection or ulceration (n (%))	5 (10)
Gastrostomy (n (%))	5 (10)
Non-skin Cancer (n (%))	3 (6)
Skin neoplasm (n (%))	3 (6)
Miscellaneous (n (%))	7 (14)
Past diseases (n (%))	27 (54)
Bone fractures in the previous 5 years (n (%))	10 (20)
Pneumonia in the previous 5 years (n (%))	10 (20)
Lower urinary tract infection in the previous year (n (%))	10 (20)
Kidney or bladder disease (urinary infection apart) (n (%))	3 (6)
Stroke (ischemic or hemorrhagic) (n (%))	2 (4)
Skin neoplasm (n (%))	1 (2)
Pulmonary embolism (n (%))	1 (2)
Lung disease (pneumonia and embolism apart) (n (%))	1 (2)
Miscellaneous (n (%))	6 (12)

Abbreviations: PD, Parkinson's disease.

Use of health resources

Most patients lived in their home and the majority had an informal caregiver. Patients seldom visited doctors, as the number of visits included those to get prescriptions only, and the use of other health resources was low **(Table 6)**.

Table 6. Use of health resources in late-stage PD patients

	PD patients (n = 50)
Patients living in their home (n (%))	35 (70)
Patients living in their relatives' home (n (%))	7(14)
Patients living in a nursery home (n (%))	8 (16)
Patients with an informal caregiver (n (%))	45 (90)
Patients with a paid caregiver (n (%))	19 (38)
Patients with both informal and paid caregiver (n (%))	14 (28)
Patients visited at State-owned hospitals (n (%))	43 (86)
Patients visited at private clinics (n (%))	3 (6)
Patients visited at State-owned hospitals & private clinics	4 (8)
Visits to family physician in the preceding 6 months (includes visits to get prescription only) (mean (SD))	2.2 (3.0)
Visits to neurologist in the preceding 6 months (includes visits to get prescription only) (mean (SD))	1.7 (1.0)
Hospital admissions in the preceding 12 months (mean (SD))	0.78 (1.0)
Patients using a physiotherapist (n (%))	10 (20)
Patients using a speech therapist (n (%))	3 (6)
Patients using a homecare nurse (n (%))	3 (6)

Abbreviations: PD, Parkinson's disease; SD, standard deviation

Caregivers

Mean time per week spent in informal caregiving was 5 days (SD±2.57), this meaning 5 days x 24 hours/week. Informal caregivers rated the impact of PD in their life as high (mean score 3.5; SD±0.8), which was significantly correlated with the LHS total score (r = - 0.5; $p < 0.01$). The domains of LHS that resulted in a statistical significant association with caregiver burden were "Mobility" (r = - 0.30) and "Orientation" (r = - 0.4)($p < 0.05$).

DISCUSSION

Handicap was assessed in a cohort of LS-PD patients and it was found that the LHS was useful and easy to apply in these patients. This cohort of LS-PD patients was highly handicapped. Handicap was strongly associated with the presence of dementia (DSM-IV), the severity of mental problems and the severity of parkinsonism in *off*. These independent variables explained more than half of the variance in the LHS total score. Furthermore, these patients were highly dependent on caregivers who spent much time in care, which resulted in a high burden for caregivers. Overall, health resources were used infrequently.

Handicap

Data about the health burden of PD obtained from patients' perspective are essential to understand the impact of disease on patients, complement the data obtained through observer-based instruments and are useful also to assess the effectiveness of therapeutic interventions. The most commonly used subjective outcome measures in PD research have been the perceived HS, generic QoL scales and the health-related QoL (HRQoL).[101] We have explored the concept of handicap for several reasons:[125,129] handicap is the central aim of rehabilitation,[128] which is crucial in progressive and chronic diseases as PD; although intimately related to the concept of (HR)QoL, its definition is more objective though keeping the subjective perspective and social interaction context as (HR)QoL does; it is a focused and concrete concept, easily understandable to patients and caregivers; it is a relevant outcome despite being mostly limited to the context of health experience. Besides, there is good transcultural agreement on the construct of handicap[133] and the objectivity of the concept allows caregivers to fill in the questionnaires in those cases where patients are incapable to do so. In our study, LHS was easily completed by patients and caregivers. The scores had a normal distribution and no ceiling or floor effects.

Dementia (DSM-IV), the severity of mental problems assessed by UPDRS part I[108,112] and the severity of parkinsonism in *off* according to the H&Y explained a major percentage of the variance in the total LHS score. The H&Y staging is deeply anchored on postural instability, but it also reflects severity of bilateral parkinsonism.[82] Indeed, others have also found that postural instability is among the most disabling problems in advanced PD.[56-58, 105,134] We previously reported severe disability in these same patients using observed-based outcome measures[119] and also assessed perceived HS. Results showed that falls and dysautonomia were the symptoms most contributing to poor perceived HS, closely followed by bradykinesia, freezing, bulbar symptoms, dementia (DSM-IV), apathy, anxiety and depression (DSM-IV).[119] Interestingly, the symptoms most associated with handicap did not fully overlap those most impacting on the HS, suggesting that handicap and HS are different constructs for patients' perception of health states. During the revision process that led to the new WHO International Classification of Functioning, Disability and Health,[135] the term *handicap* was replaced for *participation restriction*, in order to move the emphasis from consequence of disease to functioning, health and limitation of functioning. Nevertheless, the major concept that one's environment influences the functioning of an individual was still embodied in International Classification of Functioning, Disability and Health. In fact, qualitative studies showed a strong transcultural agreement on six domains of *participation*, and these corresponded to the *handicap* dimensions;[136] additionally, a study by Perenboom *et al*[137] found that 2 handicap scales from a pool of 11 existing generic instruments were the ones closest to measure solely *participation*. Indeed, one of those two scales was the LHS.

Co-morbidities and past medical conditions

PD is associated with significant co-morbidity.[138] However, this excess co-morbidity is largely confined to conditions associated with PD such as urinary complaints or to complications of PD such as bone fractures.[138] Similarly, the most frequent medical conditions of our patients were related to or complications of PD. In contrast to other studies,[138,139] stroke, cardiovascular disorders or diabetes were either low or absent, suggesting that our population may have a long survival due to the lack of potentially fatal medical conditions. 22% of our cohort reported pneumonia in the previous 5 years, a finding in accordance with data showing pneumonia as a major cause of death in

PD.[57,138,139] The finding that neither past nor concomitant diseases were associated with a higher handicap strengthens the finding of the impact of PD symptoms on the level of handicap.

Use of health resources

We expected a higher percentage of institutionalized patients, in light of the high UPDRS score, frequent falls, dementia and hallucinations in the cohort, all strong independent predictors of institutionalization.[68] Importantly, low income, the lack of availability of long-stay facilities within the health system and a family-centred organisation of Latin societies may combine to explain our findings. Keeping patients at home was accomplished at the expenses of a heavy burden of disease on caregivers and the need for a paid caregiver in many instances.

Our patients consulted doctors fewer times than those in a Dutch study, where PD patients with ≥ 8 years of disease duration made 1.9 visits to neurologist and 1.1 to family physician.[140] Admissions to hospital were few in our sample, taking into account the number of co-morbidities and the frequency of psychosis and dementia. Many of these acute medical events might be managed in emergency rooms which could explain the low rate of admissions. A minority made use of other healthcare resources such as speech therapist or homecare nurse, whereas 20% used a physiotherapy which is a low figure comparing the degree of motor involvement.[140]

Caregivers

The amount of time spent in caregiving was very high in LS-PD. Accordingly, caregivers' burden and mental health status in PD has been found to correlate significantly with weekly hours of caregiving.[141-143] Two Spanish studies found that caring for patients with disease duration of 7.6-10 years was permanent in 86-96.5% of the cases.[141-143] Caregiver time is thus an hidden cost in LS-PD, and in other cultures it would mean paid caregiver time. Caring for LS-PD patients had a strong impact on the life of caregivers and this was correlated with the LHS total score, in line with others reporting an increase in caregivers' burden with disease severity.[141-144]

Shortcomings

Our low recruitment rate perhaps indicates that there were few LS-PD cases available at the study centers, suggesting that patients withdraw from specialized medical care once they reach later stages of disease. Thus, our results may not be representative for the entire population of LS-PD. While we addressed the concept of handicap, we did not measure QoL which could have been of interest in order to compare these outcomes of HS. More information regarding caregivers could have been gathered but our aim was to obtain general data concerning caregivers' burden.

Conclusions

Handicap is an important patient-centred outcome measure which is valuable to use in LS-PD since it provides an overall measure of patients' HS and gives insight into several domains of disadvantage. The LHS proved to be easily completed and might in the future be explored in earlier stages of disease. Our results show that LS-PD is associated with high handicap and caregivers' burden, and support the notion that cognitive and behavioural symptoms, with a special emphasis on dementia, and severity of parkinsonism in particular falls and unsteadiness, should be the focus of management in later stages of PD.

CHAPTER 3: *Handicap in Advanced stage PD*

Paper:

Disability in activities of daily living and severity of dyskinesias determine the handicap of Parkinson's disease patients in advanced stage selected to DBS

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Disability in activities of daily living and severity of dyskinesias determine the handicap of Parkinson's disease patients in advanced stage selected to DBS

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Keywords: Parkinson's disease, advanced stage, handicap, London Handicap Scale, motor complications

ABSTRACT

Background: There is scarce data on the level of handicap in Parkinson's disease (PD) and none in advanced stage PD.

Objective: To assess the handicap in advanced stage PD patients with disabling levodopa-induced motor complications selected to deep brain stimulation (DBS).

Methods: Cross-sectional study of patients recruited consecutively during evaluation for DBS. Handicap was measured using London Handicap Scale (LHS) (0= maximal handicap; 1= no handicap). Disease severity was evaluated using the Hoehn & Yahr scale and the UPDRS/MDS-UPDRS, during *off* and *on* after a supra-maximal dose of levodopa. Dyskinesias were scored using the modified Abnormal Involuntary Movement Scale (mAIMS) and the Schwab and England Scale (S&E) was also scored in *off* and *on*.

Results: 100 PD patients (mean age 61 (±7.6); mean disease duration 12.20 (±4.6) years) were included. Median score of motor MDS-UPDRS was 54 in *off* and 25 in *on.* Mean total LHS score was 0.56 (±0.14). Patients were handicapped in several domains with a wide range of severity. Physical Independence and Social Integration were the most affected domains. Determinants of total LHS score were MDS-UPDRS part II *off* (β= - 0.271; p=0.020), mAIMS *on* (β= - 0.183; p=0.042), and S&E *on* (β= 0.264; p=0.005) and *off* (β= 0.226; p=0.020) scores (R^2 =29.6%).

Conclusions: LHS was easy to apply in advanced stage PD patients. Patients were moderately-to-highly handicapped and this was strongly determined by disability in ADL and dyskinesias. Change in handicap may be a good patient-centred outcome to assess efficiency of DBS.

INTRODUCTION

Level of handicap in Parkinson`s disease (PD) has rarely been assessed. Previously, we have measured the level of handicap experienced by late stage PD (LS-PD) patients using the London Handicap Scale (LHS).[125,130,145] We found that handicap was a valuable patient-centred outcome (PCO) in LS-PD and that the LHS was easily completed by patients and caregivers despite the presence of severe disability.[145] This raised the question whether handicap would also be a valuable measure of the health condition and participation of an individual in less advanced stages of PD, such as patients with disabling levodopa-induced motor complications (MC).

The World Health Organization (WHO) has recently replaced the term *handicap* with *participation restriction* to avoid any negative connotations associated with the term handicap and to emphasize that the ability of an individual to participate in everyday life situations is limited, not only by the effects of disease, but also contextual factors.[135] Nevertheless, the operational definition of handicap still holds true for clinical research since it was found that the 6 domains of participation that can be potentially affected by health states correspond to the 6 common dimensions of handicap.[135,137] Indeed, even though the LHS was developed using the definition of handicap, it accurately measures the WHO definition of participation restriction.[127,137] Furthermore, handicap is a closely defined and focused concept which retains the subjective perspective and social interaction context of quality of life (QoL), and it is easily understandable to patients and caregivers.[125] Finally, there is good cross-cultural agreement on the construct of handicap allowing for comparison between different populations, and the wide use of the LHS allows for comparison between different disease populations.[126,130,133] Reducing handicap is a central aim of therapeutic interventions, and a better understanding of the causes of handicap allows for improved adjustment of interventions and assessment of their effectiveness.[125]

Our aim was to study the handicap in *advanced stage* PD, which is widely defined as PD in patients manifesting levodopa-induced MC.[45] To enrich our sample with patients suffering from very disabling levodopa-induced MC, we enrolled PD patients selected to receive deep brain stimulation (DBS).

PATIENTS AND METHODS

Objective:

To establish the pattern and level of handicap in advanced stage PD patients with disabling levodopa-induced MC selected to DBS, and to identify the contributing factors.

Design: Cross-sectional study

Participants:

Inclusion criteria for the study were: 1) PD patients with disabling levodopa-induced MC who were given DBS in our centre; 2) completion of LHS. PD was diagnosed according to the UK Parkinson's Disease Society Brain Bank Criteria.[146] Eligibility criteria for DBS were: a) PD patients with disabling levodopa-induced MC refractory to best medical therapy; b) age below 70 years; c) a positive motor response to a levodopa challenge test (> 33% improvement after the intake of patients' usual morning levodopa equivalent dose plus 50%- a supra-maximal dose of 150%); d) lack of postural instability and freezing of gait during *on* period; e) absence of dementia associated with PD according to a formal neuropsychological assessment and unstable psychiatric disorder according to a formal psychiatry assessment; and f) lack of significant brain changes, namely atrophy or concurrent brain disorders such as vascular lesions on CT and MRI scan. Participants gave their informed consent to participate and the study was conducted according to the Declaration of Helsinki.

Participants' assessment

PD patients were recruited consecutively during routine evaluation for DBS from 2006 to April 2015, and data were collected prospectively. The results of this study pertain to the assessment before DBS. After the development of the new Movement Disorders Society-Unified Parkinson's Disease Rating Scale[147] (MDS-UPDRS), we have introduced this new scale in the routine assessment for DBS instead of the UPDRS.[94] Thus, severity of motor symptoms were evaluated using the motor part (part III) of the UPDRS and more recently the motor part (part III) of the MDS-UPDRS, and the Hoehn & Yahr (HY) scale.[42,94,147] Part III of the UPDRS\MDS-UPDRS and the HY staging were assessed during *off* period and after the intake of a supra-maximal dose of levodopa (see above) during the *best on* state. O*ff* period assessment was performed at least 12 hours after the last levodopa dose, 48

hours after the last intake of dopamine agonists, controlled-release levodopa, selegiline or rasagiline and 12 hours after the last intake of entacapone. The levodopa equivalent daily dose (LEDD) was calculated according to reported conversions.[148] Non-motor symptoms were assessed using Part I of UPDRS\MDS-UPDRS, and disability and independence in activities of daily living (ADL) were evaluated using Part II of UPDRS\MDS-UPDRS and the Schwab and England Scale (S&E).[95] The scores of UPDRS parts II and III were converted to the scores of MDS-UPDRS parts II and III according to published formula.[149] Severity of levodopa-induced MC were evaluated using part IV of UPDRS\MDS-UPDRS, and the severity of dyskinesias was scored using the modified Abnormal Involuntary Movement Scale (mAIMS) in *off* and *on* state.[150] The mAIMS was scored during rest (mAIMS rest) and counting backwards (mAIMS count). The Mini Mental State Examination (MMSE) was also performed as part of the formal neuropsychological assessment.[99]

Handicap was assessed using the LHS which consists of a self-completed questionnaire and it takes around 10 min to be completed.[130] The questionnaire has six questions, one for each domain of handicap (mobility, physical independence, occupation, social integration, orientation and economic self-sufficiency), and each question contains six sentences hierarchically describing the level of handicap; for each question, the patient must choose the most suitable sentence. Each sentence is assigned a scale weight. The questionnaire comprises a matrix of scale weights which when combined give a total score for handicap, to which a constant value of 0.456 is added. The final score ranges from 0 (maximal handicap) to 1 (no handicap).

Statistical analysis

Data analysis was performed with R software (version 2.13). A descriptive analysis was performed and the results expressed as mean ± standard deviation or percentages. The total score of the LHS was entered as a dependent variable in linear regression analysis. Multiple linear regression analysis, adjusted for age and gender, was performed to calculate which variables contributed significantly to higher levels of handicap (the lower the total score of the LHS the higher the level of handicap). The following independent variables were entered: gender, duration of the disease, scores of the MDS-UPDRS part II *on* and *off* and MDS-UPDRS part III *on* and *off*, HY stage *on* and *off,* S&E score *on* and *off*,

scores of mAIMS rest *on* and *off* and mAIMS count *on* and *off,* and the LEDD. We used both-stepwise regression to select significant variables from the original model. Statistical significance was considered for $p < 0.05$. Coefficients and 95% confidence intervals (CIs) are reported.

RESULTS

One-hundred sixty-six patients were given DBS at our centre from 2006 to April 2015. Missing entries in the LHS of 66 patients precluded the inclusion of those patients in the analysis, thus LHS data from 100 patients (63 males) were available to analysis. There were no significant differences between demographic or clinical data of patients included and not included in the study (data not shown). At the time of surgery, mean age of patients was 61 (±7.6) years and mean disease duration was 12.20 (±4.6) years **(Table 1)**.

Table 1: Demographic and clinical characteristics of advanced PD patients (n = 100)

Demographics	
	Mean (SD)/Median(min-max)
Age, years	61 (7.6)
disease duration, years	12.20 (4.6)
Gender: male (n(%))	63 (63.6%)
Clinical Characteristics	
Response in levodopa challenge test,%	57.89 (14.83)
MDS-UPDRS I (n=43)	5 (0-29)
MDS-UPDRS II *on*	15 (0-30)
MDS-UPDRS II *off*	22 (5-41)
MDS-UPDRS III *on*	25 (3-48)
MDS-UPDRS III *off*	54 (26-95)
MDS-UPDRS IV (n=43)	9.50 (0-18)
UPDRS I (n=57)	3 (0-6)
UPDRS IV (n=57)	8 (0-20)
S&E *on*	90 (0-100)
S&E off	50 (0-100)
HY *on*	2 (0-4)
HY *off*	2.50 (0-5)
mAIMS rest *off*	0 (0-10)
mAIMS count *off*	0 (0-11)
mAIMS rest *on*	4 (0-17)
mAIMS count *on*	8 (0-21)
MMSE	28 (22-30)

As parts I and IV of UPDRS are not converted to MDS-UPDRS, the table indicates how many patients have completed parts I and IV of UPDRS and parts I and IV of MDS-UPDRS

Abbreviations: PD, Parkinson's disease; (MDS)-UPDRS, (Movement Disorders Society)-Unified Parkinson's disease Rating Scale; S&E, Schwab and England scale; HY, Hoehn and Yahr; mAIMS, modified Abnormal Involuntary Movement Scale; MMSE, Mini Mental State Examination; SD, standard deviation

LHS values followed a Gaussian distribution, with a median total score of 0.509 (0.21-1.00) and a mean of 0.56 (±0.14) **(Table 2)**. No ceiling or floor effects were noted. Female

and male patients were equally handicapped. There was a wide range of responses between the different levels of disadvantage for each domain of handicap, which indicated that the LHS could discriminate well between patients. However, the most common categories within each domain of the LHS were “quite a lot” and “very slightly” disadvantage, with fewer subjects scoring in the “almost completely” and “completely” disadvantage categories. DBS patients were handicapped over several domains of the LHS. The domains for which more patients scored a greater disadvantage (“very much”, “almost completely” and “completely”) were Economic Self-sufficiency (n=26), Occupation (n=25) and Mobility (n=10). The Physical Independence sub-score ($r = 0.777$, $p < 0.001$) and the Social Integration sub-score ($r = 0.657$, $p < 0.001$) showed the greatest association with the LHS total score, thus these were the most severely affected domains, closely followed by the Mobility sub-score ($r = 0.634$, $p < 0.001$). In multiple linear regression analysis, using the LHS total score as the dependent variable, 2 models were the most informative. In model 1, the independent variables that were most associated with handicap were the scores of MDS-UPDRS part II *off* ($\beta = - 0.271$; $p = 0.020$), mAIMS count *on* ($\beta = - 0.183$; $p = 0.042$), and S&E *on* ($\beta = 0.264$; $p = 0.005$) and *off* ($\beta = 0.226$; $p = 0.020$) **(Table 3)**. This model R^2 was 29.6%. In model 2, the LEDD variable was replaced by the dose of each antiparkinsonian drug used in our population and the presence/absence of dopamine agonists. The dose of entacapone came out significant in model 2 ($\beta = - 0.223$; $p = 0.014$), but a R^2 of only 1.4 was gained (31%).

Table 2: Total and sub-scores of London Handicap Scale and correlations with total scores

	Mean (SD)	Median (Min,max)	Minimum / Maximum possible values for total score and sub-score	Pearson correlation with total score	*p*-value for correlation
Social Integration	0.021 (0.028)	0.035 (-0.029, 0.630)	-0.041 / 0.063	0.657	<0.001
Orientation	0.055 (0.064)	-0.109 (-0.063, 0.109)	-0.075 / 0.109	0.473	<0.001
Economic self sufficiency	0.035 (0.043)	0.033 (-0.111, 0.100)	-0.111 / 0.100	0.522	<0.001
Mobility	0.019 (0.033)	0.000 (-0.036, 0.071)	-0.108 / 0.071	0.634	<0.001
Physical Independence	0.004 (0.056)	0.011 (-0.057, 0.102)	-0.061 / 0.102	0.777	<0.001
Occupation	-0.004 (0.039)	-0.014 (-0.060, 0.099)	-0.060 / 0.099	0.428	<0.001
Total	0.585 (0.152)	0.567 (0.274, 1.000)	0 / 1	NA	NA

Abbreviations: SD, standard deviation; NA, not applicable

Table 3: Regression model for the London Handicap Scale

	β Coefficients	95% CI for β		t-test	*p*-value
MDS-UPDRS II *off*	-0.271	-0.007	-0.001	-2.834	0.006
Schwab & England *on*	0.264	0.001	0.004	2.902	0.005
Schwab & England *off*	0.226	0.000	0.003	2.370	0.020
mAIMS count *on*	-0.183	-0.009	0.000	-2.066	0.042

Abbreviations: MDS-UPDRS, Movement Disorders Society-Unified Parkinson's disease Rating Scale; mAIMS, modified Abnormal Involuntary Movement Scale; CI, confidence interval

DISCUSSION

Handicap was assessed in advanced stage PD patients with disabling levodopa-induced MC prior to DBS implant, using the LHS which was found to be an easy to apply tool in these patients. The study population was moderately-to-highly handicapped, and the level of handicap was strongly determined by the disability and independence in ADL, and the severity of peak-dose dyskinesias during the levodopa challenge test. These independent variables accounted for one-third of the patients' handicap.

We have previously reported the assessment of handicap, using the LHS, in a population of LS-PD patients.[145] We found that handicap was a valuable PCO in LS-PD and the LHS was easily completed even in those very disabled patients.[145] We now add findings on the assessment of handicap, using the LHS, in PD patients that are in a less advanced stage than LS-PD. We chose patients selected to DBS because they are the prototype of patients with disabling MC, which is the more widespread definition of *advanced stage* PD.[45] We are aware though that DBS patients are a sub-group of PD patients with MC, but we aimed to study that pure sample of patients with MC. Additionally, we aimed to explore handicap and the LHS as a PCO of patients' health condition in DBS patients to test in future whether it may be sensitive to change after surgery.

The overall handicap of DBS patients was lower than that of LS-PD patients, who had a mean LHS total score of 0.338 (± 0.155).[145] This suggests that DBS patients, although manifesting very disabling MC, are less handicapped than more advanced PD patients whose clinical picture is dominated by motor and non-motor symptoms which are poorly responsive to L-dopa.[57,145] On the other hand, the level of handicap of DBS patients was greater than that reported for stroke survivors at 6 months, 2 and 5 years whose mean LHS score ranged from 0.73 to 0.93.[151-153] Unfortunately, there is no data regarding handicap in other neurodegenerative disorders to compare with, such as Alzheimer's disease or amyotrophic lateral sclerosis. The Physical Independence and Social Integration domains were the most severely affected in our patients. Disadvantage in Physical Independence reflects an inability to look after oneself in tasks such as housework, shopping, looking after money, getting dressed and using the toilet, while disadvantage in Social Integration reflects an inability to meet family, friends and other people during a normal day.[130] Our results show that patients with disabling MC are highly handicapped

when it comes to looking after themselves independently and conducting a healthy social life. Due to the surgery criteria, patients selected to DBS could not have dementia, which may explain why Orientation was not a severely affected domain, when this was the most handicapped domain seen with LS-PD patients who had a high frequency of dementia.[145] It seems that LS-PD patients are a particular and distinct sub-group of advanced stage PD.[145] DBS patients also differ from stroke survivors who are most affected in domains that are more motor dependent (Mobility, Physical Independence and Occupation).[152,153] Factors associated with greater handicap were the disability and independence in ADL (MDS-UPDRS part II and the S&E scale) and the severity of peak-dose dyskinesias. This reflects how motor impairment impacts on ADL in this sample of DBS patients and why Physical Independence and Social Integration were the most affected domains of LHS. Interestingly, the score of MDS-UPDRS part II in *off* but not *on* was correlated with level of handicap, suggesting that the severity of disability when patients are in *off* period may better translate the severity of PD. Also of interest, neither the MDS-UPDRS motor part nor the response to levodopa or the LEDD correlated with level of handicap, probably because they were very homogeneous between patients. However, peak-dose dyskinesias predicted greater handicap in DBS patients. Indeed, they are a major indication for DBS because of the disability they cause.[81,154] Unexpectedly, parts IV (motor complications) of UPDRS and MDS-UPDRS were not significantly associated with the LHS, probably due to the small sample size of patients completing either the UPDRS or the MDS-UPDRS as the scores of UPDRS part IV are not possible to convert to MDS-UPDRS.[149] However, it may also suggest that dyskinesias should be scored during the levodopa challenge test when selecting patients for DBS. Additionally, LHS score was not predicted by part I (non-motor symptoms) of UPDRS/MDS-UPDRS, which may be related to the absence of dementia, psychosis or unstable psychiatric disorders in patients selected for DBS or, alternatively, due to small sample size as mentioned above for part IV of UPDRS\MDS-UPDRS.

QoL and health-related QoL ((HR)QoL), a concept intimately related to, but distinct from, handicap, is similarly poor in PD patients with MC.[40,47,48,125,155,156] Data suggest that motor fluctuations might have a stronger impact than dyskinesias on HR(QoL), and that the level of disability associated with dyskinesias might vary according to severity of PD.[47,48,155,156] However, (HR)QoL scales are not very sensitivity to change in disease progression over

time in PD.[157] Handicap might thus be an alternative candidate as a PCO to measure change after DBS. Additionally, handicap is a concept easily understood by patients and caregivers, and more closely defined and focused than QoL.[125]

Our study has some limitations. If all patients had completed either the UPDRS or the MDS-UPDRS, the study would have more power to test the contribution of parts I and IV of these scales to the level handicap of patients. We did not enrolled patients with disabling MC that were excluded from DBS after assessment. In these patients, the severity of handicap and its contributors might have differed from the patients we included. Finally, it would have been interesting to use a (HR)QoL scale to assess our patients, to permit a head-to-head comparison between handicap and (HR)QoL ratings. This would be particularly interesting when assessing the responsiveness of handicap scales to DBS.

In conclusion, we were able to use handicap to measure overall health condition and individual's participation in advanced PD patients with disabling levodopa-induced MC selected to DBS. The LHS was easily completed by patients and we have now values for the LHS in advanced and late-stage PD patients. Further studies are now needed to assess how sensitive the LHS is to measure changes in handicap after DBS.

CHAPTER 4: *Concept and a proposal for a definition of Late-Stage PD*

Paper:

Late-stage Parkinson Disease

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Late-stage Parkinson disease

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ABSTRACT

The cardinal symptoms of Parkinson's disease (PD) are asymmetrical bradykinesia, rigidity, resting tremor and postural instability. However, the presence and spectrum of, and disability caused by, non-motor symptoms (NMS) are being increasingly recognized. NMS include dementia, psychosis, depression and apathy, and are a major source of disability in later stages of PD, in association with axial symptoms that are resistant to levodopa therapy. The model of clinical progression of PD should, therefore, incorporate NMS, instead of being restricted to motor signs and levodopa-induced motor complications. Patients with disabling motor complications are classified as having advanced PD, which has been thought to represent the ultimate stage of disease. However, deep brain stimulation to treat motor complications has dramatically changed this scenario, with implications for the definition of advanced stage disease. As treatment improves and survival times increase, patients are increasingly progressing to a later phase of disease in which they are highly dependent on caregivers, and disability is dominated by motor symptoms and NMS that are resistant to levodopa. In this article, we review the changing landscape of the later stages of PD, and propose a definition of late-stage PD to designate patients who have progressed beyond the advanced stage.

INTRODUCTION

Parkinson's disease (PD) is the second most common age-related neurodegenerative disorder after Alzheimer disease. PD occurs worldwide with an age-adjusted prevalence of 1.8% and similar incidences in females and males.[29] The mean age of onset is about 65 years, with prevalence rising from 0.6% at age 65–69 years to 2.6–3.5% at age 85–89 years.[29-30] Disability in this disease is progressive[158] and associated with increased mortality (relative risk of death 1.6–3.0 compared with matched control populations).[8, 31]

The primary pathology of PD is progressive dopaminergic neuronal loss in the substantia nigra, but other neurotransmitter systems (cholinergic, noradrenergic and serotonergic) are also affected.[9,10] Clinically, PD is characterized by the motor symptoms of asymmetrical bradykinesia, rigidity and rest tremor, as well as postural instability later in the disease course.[33] However, non-motor symptoms (NMS) such as dementia, depression, pain, sleep disorders and dysautonomia increase in frequency and severity in later disease stages.[34] The available pharmacological and surgical treatments substantially improve motor symptoms, but achievement of satisfactory symptomatic control becomes difficult in more-advanced disease stages. Levodopa remains the most potent antiparkinsonian drug, but its long-term use is associated with development of motor complications.[35,40]

This Review discusses data regarding the phenotype of later stages of PD, including the widely accepted advanced stage PD, which features motor complications, and the less-well characterized subsequent stages, which feature disability 'milestones' in the approximately 5 years preceding death. We focus on the changing landscape of later stages of PD over the past decade, and discuss the emerging concept of late-stage PD. Such aspects of PD are becoming increasingly relevant as neurologists are more often treating patients with very-advanced stage PD owing to improved treatment and increased survival.

PROGRESSION OF PD

Traditionally, progression of PD is regarded as an increase in severity of motor symptoms—which can be either levodopa-responsive or levodopa-resistant[54,55] — together with the emergence of levodopa-induced motor complications.[39] This motor progression is nonlinear, with a more rapid decline in motor function in earlier stages

compared with later stages.[55,159] A recent study found that an increase of 2.5 points in the motor Unified Parkinson Disease Rating Scale (UPDRS) score,[94] or of 4.3 points in the total UPDRS score, is the minimum change required to be recognized by patients as being clinically significant.[160]

Motor complications

Most patients with PD who receive dopaminergic therapy go on to develop motor complications.[50,161] The frequency of this phenomenon varies among studies, but seems to affect about 40–50% of patients after 4–6 years of levodopa treatment.[39] Occurrence of motor complications is most strongly related to disease duration, and to duration and dose of levodopa treatment.[39,155] However, in the ELLDOPA trial, a substantial number of patients developed motor complications within 9 months of levodopa treatment.[87] In advanced stages of PD, motor complications have a considerable impact on quality of life (QoL) and patient disability.[40,47] The domains of QoL that are most affected seem to be mobility, activities of daily living (ADL), stigma and communication.[40] Interestingly, in patients with disease duration of 5–10 years, a higher levodopa dose was associated with better QoL despite an increased prevalence of motor complications.[155] Compared with the general population, PD patients with motor complications had a worse QoL, which deteriorated substantially with disease severity.[162] However, in later disease stages, disability from motor complications seemed to decline relative to disability associated with symptoms that are resistant to levodopa.[56,57,119] Some studies even found that motor complications remitted in some patients[59,119]—a finding that did not correlate with a reduction in the dose of antiparkinsonian drugs.

Levodopa-resistant symptoms

The clinical progression of PD in later stages is increasingly recognized to be dominated by the emergence or aggravation of symptoms that are nonresponsive to levodopa.[56,57,65,90,163,164] These can include NMS such as dementia, psychosis or dysautonomia, and axial motor symptoms such as falls, postural instability or dysphagia. These symptoms are the main determinants of QoL, and are a major source of disability, as well as being risk factors for institutionalization and death.[56,57,59,65,119,163-166] As such, NMS and axial motor symptoms that are resistant to levodopa should be incorporated into the classic model of PD progression.

Sequence of events

Some motor symptoms and NMS tend to progress together, and a study found that a cluster of variables consisting of NMS (cognitive impairment, psychosis, depression, daytime sleepiness, autonomic dysfunction) and axial symptoms was strongly associated with disease progression.[134] These findings suggest that, together, NMS and axial symptoms dominate the clinical picture of late stages of PD, and that they share common pathogenic mechanisms. Intuitively, one thinks that PD starts with prodromal symptoms,[167] followed by unilateral and then bilateral motor symptoms, progressing to motor complications, balance and gait impairments, and finally psychosis and dementia.[1,57] This sequence of events is not, however, a universal rule, although we cannot yet predict with much certainty which patients will, for example, develop dementia before motor complications.

STAGING OF PD

For several decades, attempts have been made to stage the clinical evolution of PD.[42] In the pre-levodopa era, Hoehn and Yahr developed a staging system to describe clinical function at different stages of disease, including the concepts of disability (functional deficits) and impairment (objective signs).[42,82] The Hoehn and Yahr scale was based on the concept that the severity of parkinsonism depended mainly on the presence of bilateral symptoms and compromise of gait and balance, and that physical independence was ultimately lost owing to postural instability, gait disorder and severe bilateral parkinsonism.[42,82] This scale has been the most widely used tool to stage the severity of parkinsonism,[83] and available data show significant correlations between later Hoehn and Yahr stages and worse scores for QoL and motor impairment.[85,86]

In addition to physical signs, the Hoehn and Yahr scale can capture other important features of PD: when patients reach stage 3, risk of dementia is increased and survival decreases, and total UPDRS scores increase despite drug adjustment.[82,84] Advanced PD is commonly defined as stages 4 and 5 on the Hoehn and Yahr scale, which corresponds with loss of physical independence.[82]

Some weaknesses of the Hoehn and Yahr scale can bias its use. First, incorporation of two indices of severity —impairment and disability—can create ambiguity and difficulty in classifying individual patients, as these indices do not necessarily progress in parallel and

may even diverge. Second, the indices are particularly sensitive to postural instability and disorders of lower limbs, thereby increasing the likelihood of overlooking disease progression that is attributable to other motor symptoms or NMS. Last, the Hoehn and Yahr scale broadly categorizes rather than finely grading disease stages, such that an increase in stage does not necessarily entail an overall increase in the patient's motor dysfunction in all cases. As such, patients of different impairment severity can be assigned to the same stage of the Hoehn and Yahr scale, creating clinical heterogeneity in each category.[82]

Overall—and despite its weaknesses—the Hoehn and Yahr scale remains the most robust staging system for PD. Nevertheless, in order to capture the multidimensional causes of disability in later stages of PD, criteria other than the Hoehn and Yahr scale might be needed to define such disease stages, as discussed below.

As an alternative to the Hoehn and Yahr scale, the definition of advanced stage PD has rested on the presence of motor complications, as their occurrence increases with disease duration and severity, and they are a major source of disability.[40,51,168] In this staging system, patients are usually classified as having advanced stage disease once motor complications begin,[59] or when these symptoms become severe enough to substantially impair QoL and independence in ADL.[45] A different definition of advanced stage PD was recently proposed,[169] which encompasses patients manifesting the cardinal motor symptoms of PD, together with disease-related or drug-induced motor and non-motor complications. This definition has the advantage of combining disease-related and drug-related symptoms with motor symptoms and NMS in the criteria for advanced PD.

ADVANCED-STAGE PD: A MOVING CONCEPT

The advent of deep brain stimulation (DBS) has radically advanced the treatment of motor complications and, therefore, the phenotype and natural history of advanced PD.[74, 170]

DBS is a powerful therapeutic intervention for advanced PD, leading to substantial reductions in motor symptoms and motor complications, doses of antiparkinsonian drugs, and disability.[74,75,88] DBS also increases QoL of patients with PD[171-173] and, more recently, was found to be superior to best medical therapy for the treatment of motor complications.[75,173,174] This motor improvement is sustained overall at 10 years after DBS

of the subthalamic nucleus, with the exception of axial signs, which progressively worsen over time.[76]

DBS is neither curative nor neuroprotective, and cannot, therefore, arrest neurodegeneration and clinical progression. In the long term, patients who have received DBS deteriorate owing to axial, cognitive, and behavioural symptoms that are not responsive to treatment.[74,76, 88]

ADVANCED STAGE VERSUS LATE-STAGE PD

Heterogeneity in advanced stage PD

The classic concept of advanced stage PD is broad and, depending on the definition used, encompasses patients with bilateral disease, postural instability and physical dependence (according to Hoehn and Yahr staging) and/or patients with motor complications. Considerable heterogeneity exists among patients with advanced stage disease, owing to variations in the predominance and severity of motor symptoms and NMS, and in the presence and severity of motor complications, as well as the possible use of DBS.

Disease duration is thought to be a key determinant of the stage of progression, but baseline characteristics of patients with advanced PD who were enrolled in clinical trials for motor complications and PD-associated dementia **(Table 1)** suggest the involvement of other factors and considerable heterogeneity between patients at this stage of disease.[75,173-176] These data also highlight the fact that the sequence of events is not universal for all patients and that a subset of patients categorized under the term ‘advanced disease’ do not fulfil the usual definition of advanced PD. More-nuanced definitions of the late stages of PD are, therefore, needed.

Table 1 Baseline features of patients in trials for drug-induced MC and PD-associated dementia

Parameter	Clinical trial of drugs for MC	Clinical trials of deep brain stimulation for MC			Clinical trials for PD-associated dementia			
	Rascol *et al.* (2005)[175]	Deuschl *et al.* (2006)[75]	Weaver *et al.* (2009)[174]	Williams *et al.* (2010)[173]	Aarsland *et al.* (2009)[177]	Leroi *et al.* (2009)[178]	Emre *et al.* (2004)[179]	Emre *et al.* (2010)[176]
Mean age at PD onset (years)	55.0	47.0	50.0	47.6	69.5	65.9	63.0	65.5
Mean age (years)	64.0	60.5	62.3	59.0	76.5	75.7	72.0	72.5
Mean disease duration (years)	9.0	13.5	12.4	11.4	7.0	9.75	9.0	7.0
UPDRS motor score during 'on' time	23.6	18.0	23.0	19.5	11.2*	24.2	34.0	30.0
Mean levodopa treatment duration (years)	7.5	13.5	11.7‡	NA	NA	NA	NA	NA

*Modified motor UPDRS, score range 0–32. ‡Anti-PD drugs, not necessarily levodopa. Abbreviations: MC, motor complications; NA, not available; PD, Parkinson disease; UPDRS, Unified Parkinson Disease Rating Scale.

The concept of late-stage PD

Evidence suggests that at least a small subset of patients with advanced stage PD will progress to a later phase of disease **(Figure 1)**. In this latter stage, disability from motor complications is reduced, because these complications attenuate either naturally or in response to DBS.[57] Disability in the later stage is dominated by levodopa-resistant motor symptoms and NMS,[56,180,181] so that patients no longer fit the classic definition of advanced stage disease, which is characterized by disabling motor complications. Patients with late-stage PD present with a distinct phenotype, which seems more homogeneous than that denoted by the generic name of advanced stage disease. They require specialist medical care,[56] although they are usually excluded from clinical trials and even from observational studies.

On the basis of our research in patients who progress beyond advanced PD,[119] we propose the term 'late-stage' to describe patients who are highly dependent on caregivers for ADL, owing to treatment-resistant motor symptoms or NMS. For this definition, we use the Schwab and England ADL Scale,[95] which is a questionnaire that measures patients' perceived functional independence. Scoring ranges from 0% (denoting a bedridden or vegetative state) to 100% (denoting normal ability with complete independence), with 10% increments. The scale is easy to apply, has moderate to substantial validity and good reliability, and correlates well with UPDRS motor scores.[182,183] Furthermore, the sensitivity of the Schwab and England scale tends to increase with higher Hoehn and Yahr stages, thus requiring smaller sample sizes to compare patients in more-advanced Hoehn and Yahr stages.[182]

Our proposed operational definition of late-stage PD is a score on the Schwab and England Scale of less than 50% during periods of adequate symptom control ('on' period). A score of 50% corresponds with the patient requiring help with half of their chores and experiencing difficulty with all activities. A score of 40% corresponds with the patient being highly dependent on support from carers, able to assist with all chores, but unable to complete most tasks alone.[95]

We are aware that the designation of 'late-stage' to define the ultimate phase of PD deserves further discussion by clinicians, researchers and patients in order for all parties to reach consensus on its appropriateness, understandability and utility. We think that

the Schwab and England Scale and a 50% threshold are suitable, but discussion and validation is also required.

Figure 1. Progression of PD in the post-levodopa and deep brain stimulation era

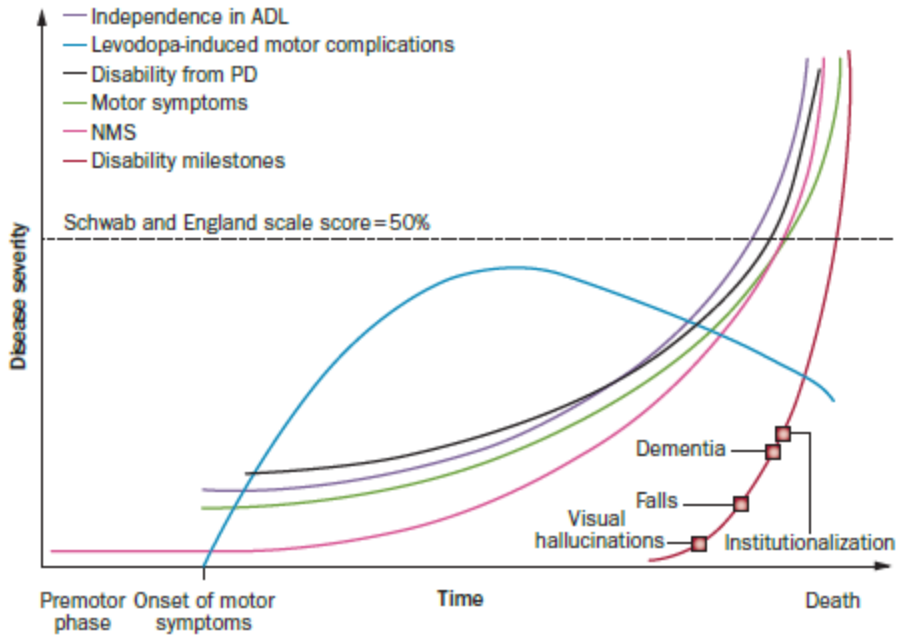

Figure 1 | Progression of PD in the post-levodopa and deep brain stimulation era. A premotor phase of PD is followed by onset of motor symptoms. Over about 5 years, motor symptoms progress in parallel with disability and loss of independence in ADL. During this phase, NMS also progress, but at a slower pace than do motor symptoms. When levodopa-induced motor complications emerge, they become a major source of disability and loss of independence in ADL. The severity of motor complications declines in later stages of PD owing to deep brain stimulation and/or natural resolution. Concomitantly, NMS, bradykinesia and axial motor symptoms that are resistant to levodopa begin to rapidly increase in severity, accompanied by increased disability and loss of independence. Approximately 5 years before death, disability 'milestones', such as visual hallucinations and dementia, emerge in an exponential manner. Abbreviations: ADL, activities of daily living; NMS, nonmotor symptoms; PD, Parkinson disease.

Clinical phenotype of late-stage PD

Both cross-sectional and longitudinal data show that disability in more-advanced stages of PD is mainly determined by motor symptoms and NMS that are resistant to levodopa.[42,56-59,90,119,180,181,184] The severity and frequency of NMS seem to increase with advancing disease.[56,90,164,180,181,184,185] The PRIAMO study found that from Hoehn and Yahr stage 1 to stage 4–5, the frequency of NMS increased in 11 NMS domains (gastrointestinal, urinary, pain, sleep, fatigue, apathy, attention and memory, skin symptoms, psychiatric, respiratory, and miscellaneous), but not in the domain of cardiovascular symptoms.[180] For example, 43% of patients at Hoehn and Yahr stage 1 experienced urinary symptoms, compared with 90% of those at stage 4–5. Similarly, 61% of patients at Hoehn and Yahr stage 1 reported psychiatric symptoms, compared with 84% of patients at stage 4–5.[180]

A study on neuropsychiatric symptoms in patients with PD also found that the severity of depression, dementia and psychosis increased with disease severity.[181] Interestingly, this study found that patient age, as well as Hoehn and Yahr stage, influences disease severity. The types and relative frequencies of most neuropsychiatric symptoms, however, seem to be similar across all stages, indicating that the presence (but not the severity) of these symptoms is independent of staging.[60,106,119]

The Sydney cohort study provided 20-year follow-up data on individuals with PD who were initially enrolled in a clinical trial for levodopa-naive patients.[56,57] In a report of outcomes at 15 years,[56] prevalence figures were 81% for falls, 79% for daytime sleepiness, 50% each for hallucinations, depression and choking, 48% for dementia, and 41% for urinary incontinence. Among the 30 patients surviving until 20 years of follow-up,[57] falls, freezing, dementia and moderate dysarthria were each seen in over 80%, hallucinations, excessive daytime sleepiness and urinary incontinence were each experienced by more than 70%, and choking occurred in 48%. Motor complications were frequent at 20 years, affecting 95% of patients, but were not a major cause of disability.[56,57]

In fact, results from several studies suggest that the severity of motor complications decreases as disease progresses, which could explain in part the increased importance of NMS in later stages of PD.[56,59,105,119,186,187] We have reported comparable findings in our

cohort of 50 patients with PD who have a mean disease duration of 18 years.[119] The symptoms with the greatest impact on perceived health status were falls, unsteadiness, urinary dysfunction and excessive sweating.

Disability milestones in late-stage PD

Disability milestones were defined by Kempster *et al.* as symptoms of disease advancement that are likely to require additional medical attention.[105] Motor symptoms and NMS that are nonresponsive to levodopa are the most reliable predictors of nursing home placement and mortality.[56,67-69,164] The strongest independent predictors of institutionalization and death are postural instability and falls, dementia, and hallucinations.[56,67-69,163,164] Moreover, two clinicopathological studies showed that four disability milestones (visual hallucinations, falls, dementia and institutionalization) tend to cluster together in the late phase of PD and precede death by around 5 years **(Figure 1, Table 2)**.[105,188] This time-locked relationship between occurrence of these four disease milestones and death seems to be independent of age at disease onset, disease duration and age at death.[105,188] On average, the milestones preceded death by the following time intervals: 5.1 years for visual hallucinations, 4.1 years for falls, 3.3 years for dementia, and 3.3 years in the case of institutionalization.[188] The main difference between patients was the milestone-free duration of disease. Patients with earlier disease onset had longer disease duration before the occurrence of milestones and death, a stronger response to levodopa, and more-severe motor complications, whereas patients with later disease onset had a shorter disease course, a weaker response to levodopa, and no motor fluctuations.[105] Thus, a late phase of PD seems to progress in the same fashion regardless of the preceding disease course.[105,188]

Table 2: Parkinson disease disability milestones in selected longitudinal cohorts

Variable	Sydney cohort, 15 years (2005)[56]	Sydney cohort, 20 years (2008)[57]	Kempster *et al*. (2007, 2010)[105,188]	Stavanger Parkinson Project (Norwegian cohort)*
Number of patients	52	30	129	230 (in the baseline cohort)
Age	71	74	75.5	73.5 at baseline
Duration of follow-up	15.2	20	NA	16 (longest report)
Visual hallucinations				
Age at onset	66.7‡	NA	70.4‡	77.8‡ (for those with hallucinations)
Time to onset	10.7	NA	8.5‡	13.0 (for those with hallucinations)
Falls				
Age at onset	67.5‡	NA	71.4‡	NA
Time to onset	11.5	NA	9.5‡	NA
Residential home admission				
Age at admission	NA	71.6§	72.2‡	NA
Time to admission	NA	9.6§	10.5‡	NA
Dementia				
Age at onset	75.2	71.6	72.2‡	78.4
Time to onset	15.1	10.9	10.5‡	13.8
Death				
Age at death	75.5	76	75.5	81.1
Time to onset	12.2	12.4	13.7	15.8 (median)

Apart from numbers of patients, all data, unless otherwise stated, represent mean values in years. *Figures for this table were extracted from the many reports published by the Stavanger Parkinson Project. ‡We calculated these values on the basis of the data provided in the original studies. §Estimated value for initial sample. Abbreviation: NA, not available.

Late-stage PD in clinical practice

The prevalence of late-stage PD is likely to increase in the future owing to better general health care, increased longevity and better clinical management of PD.[92] Patients at this stage of disease will be a heavy burden for families and healthcare systems, and caregivers will require specialist training. Nevertheless—and perhaps importantly—patients tend to withdraw from specialized medical care once they reach a very advanced stage of PD, for reasons that remain unclear. Practising clinicians will face considerable challenges in managing these patients and their caregivers.

Clinical assessment and therapeutic management of patients with late-stage PD should focus on such problems as falls and postural instability, urinary dysfunction, freezing, bradykinesia, dysarthria and choking, dementia, psychosis, excessive daytime sleepiness, apathy, depression and anxiety. Treatment for motor complications should be less of a priority **(Table 3)**.[56,59,90,119,163,180-181,184-185] Clinicians should be proactive in asking patients and caregivers about NMS, as these symptoms are often not declared to healthcare professionals.[189] Differential diagnosis and rigorous ascertainment of dementia, apathy, depression and even psychosis is particularly difficult in this population, owing to severe dysarthria and daytime somnolence.[56,119,180-181,185] For other symptoms, the situation is more clear-cut: bradykinesia is usually severe whereas rigidity is either absent or mild, which could assist in making a differential diagnosis;[119] notably, reliance on the presence of rigidity could mislead judgments on the severity of parkinsonism.

Effective treatments are lacking for most levodopa-resistant symptoms. Pharmacological management is further complicated by adverse effects—namely, psychosis and excessive daytime sleepiness—induced by antiparkinsonian drugs. Management strategies should aim for regimen simplification, focusing on problematic symptoms for which efficacious treatments are available. For example, in our study of 50 patients with late-stage PD, levodopa was taken as monotherapy in 36% of patients, and 50% were taking neuroleptics, mainly clozapine.[119]

Table 3: Frequency of drug-induced motor complications and nonmotor symptoms in selected studies

Variable	Coelho *et al.* (2010)[119]	Sydney cohort, 15 years (2005)[56]	Sydney cohort, 20 years (2008)[57]	Kempster *et al.* (2010)75[188]	Kempster *et al.* (2007)[105]	Papapetropoulos *et al.* (2005)[90]	Stavanger Parkinson Project*	Katzenschlager *et al.* (2008)[190]
Motor fluctuations	39 (78)	50 (96)	30 (100)	NA	62 (64.0)	32 (47.8)	53 (22.1) at 9.1 years of PD duration	56 (53.3)
Dyskinesias	31 (62)	49 (94)	30 (100)	NA	60 (61.8)	28 (41.8)	NA	59 (56.2)
Troublesome or moderate–severe dyskinesias	13 (26)	6 (12)	3 (10)	NA	NA	NA	NA	38 (36.2)
Dementia	25 (50)	25 (48)	25 (83)	70 (54) with cognitive disability	54 (55.6) with cognitive disability	34 (50.7)	21 (46.6) of those evaluated at 12 years	27 (24.7)
Falls	25 (50)	41 (81)	27 (87)	45 (35)	32 (33.0)	39 (58.2)	NA	NA
Visual hallucinations	22 (44)	26 (50)	23 (74)	77 (61)	57 (58.7)	35 (52.2)	12 (48.0) of those evaluated at 12 years	NA
Depression	31 (62)	22 (54% of those tested)	15 (50) on antidepressant	NA	NA	29 (43.3)	19 (24.0) at 17.0 years of PD duration	NA
Urinary dysfunction	32 (64)	22 (41)	22 (71)	NA	NA	19 (28.4) had autonomic dysfunction	n/a	NA
Daytime sleepiness	18 (36)	41 (79)	21 (70)	NA	NA	NA	40 (45.0) at 16.8 years of PD duration	NA
Dysphagia	34 (68)	"Common"	15 (50) had choking	NA	NA	NA	n/a	NA
Mean UPDRS motor score (SD)	49.2 (13)	41.2 (SD NA)	NA	NA	NA	NA	47.1 (20.7) at 16.8 years of PD duration	NA

Apart from UPDRS motor scores, values shown in the table refer to numbers of patients, and values in brackets express the number of patients as a percentage of the total number of patients in the cohort. *Figures for this table were extracted from the many reports published by the Stavanger Parkinson Project. Abbreviations: NA, not available or not applicable; UPDRS, Unified Parkinson Disease Rating Scale.

Late-stage PD in clinical research

The phenotype of PD changes considerably in later stages, and the symptoms that contribute most to disability in later stages differ from those in less-advanced and early stages.[56,59,90,119,163,180,181,184,185] These changes probably reflect the dynamics of neurodegeneration over time, together with the effects of antiparkinsonian drugs.[1-2] In this sense, late-stage PD is a good clinical model to identify the symptoms that cause most disability, and even mortality, in patients who are severely disabled, highlighting the symptoms that should be targeted at an earlier stage of disease. Follow-up of patients in later stages will be valuable in estimation of the rate of motor and non-motor progression in advanced disease, which is known to differ from that in earlier stages.[168]

Pathogenesis and neuropathology of late-stage levodopa-unresponsive symptoms are key areas for future PD research. Loss of dopaminergic neurons in the substantia nigra pars compacta is considered to be the key biological substrate for the classic motor features of PD.[2] However, extranigral involvement has been extensively documented in PD, and has been implicated in the pathogenesis of levodopa-unresponsive motor symptoms and NMS.[1,188,191-193] For example, loss of cholinergic neurons in the pedunculopontine nucleus and nucleus basalis of Meynert is thought to be crucial in the pathogenesis of the cognitive impairment, attention deficit, postural instability and falls, and visual hallucinations that are observed in late-stage PD.[194,195] These emerging data have already led research to encompass neuronal systems beyond dopaminergic pathways.

The Braak staging system[1] suggests that the progression of α-synuclein accumulation follows a consistent pattern, beginning in the gut and gastric autonomic plexus of Meissner and olfactory nerve endings, ascending rostrally and ultimately reaching cortical areas. However, the presence of Lewy bodies containing α-synuclein in the cortex is neither necessary nor sufficient for impaired cognition,[192,196] which questions the validity of the Braak staging system to explain all symptoms of PD.

The importance of future research on disability milestones is twofold. First, it might promote the identification of new therapeutic targets for drug development. Second, these milestones may represent good candidates for clinical end points of future trials on disease progression.[134] Disease milestones are, however, associated with considerable problems, which merit discussion. Therapeutic interventions aimed at disease milestones may lack efficacy on functional outcomes and disability, owing to the advanced stage of

disease at which these events occur. Moreover, if such milestones are used as end points for clinical trials of disease-modifying therapies, the experimental intervention would probably have to be initiated early in the disease course to allow a reasonable follow-up time in which to measure outcome. Such lengthy trials risk a high drop-out rate, face the threat of a change in clinical management of PD, and are expensive.

CONCLUSIONS

Mounting evidence suggests that at least a subset of patients with PD will progress to a late phase of disease in which disability is dominated by levodopa-resistant motor symptoms and NMS **(Figure 1)**. This late-stage PD is characterized by a clinical phenotype that does not fit the common concept of advanced PD. Some patients who enter late-stage PD will have had longer disease duration than other patients at the same disease stage, with earlier disease onset and motor complications that may, at some point, justify DBS because of severe disability. DBS will not, however, prevent the emergence of other sources of disability as disease progresses. Another group of patients will have had a shorter disease course, with older age at onset and few or no motor complications, and this group will eventually enter late-stage PD without prior DBS.

Among the features of late-stage PD, falls, hallucinations, dementia and institutionalization represent milestones that start an exponential curve of disease progression, ending in death within approximately 5 years. Age at onset and disease duration only seem to determine how long the patient will remain milestone-free. Identification of the most disabling symptoms has direct implications for the focus of clinical care and research.

A universal feature among patients with late-stage PD is complete loss of independence. We propose that this stage of PD should designate patients who are very dependent on caregivers for ADL, scoring less than 50% on the Schwab and England Scale during the 'on' period. This definition focuses on functional consequences of motor and non-motor parkinsonism, in contrast to late stages on the Hoehn and Yahr Scale, which place emphasis on postural instability and gait dysfunction. Discussion and validation of a suitable definition of late-stage disease should be the topic of future work, to address this increasingly common facet of the PD landscape.

Review criteria

We searched PubMed for full-text papers published in English and French between January 1966 and April 2012 using the terms "Parkinson disease" and "advanced", "late stage", "staging", "progression", "nonmotor symptoms", "nondopaminergic", "environmental" and "pathology". Reference lists of identified papers were manually searched for additional relevant studies.

CHAPTER 5: Treatment of non-motor symptoms in Late-Stage PD- evidence from controlled clinical trials

Paper:

Treatment options for non-motor symptoms in late-stage Parkinson's disease

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Treatment options for non-motor symptoms in late-stage Parkinson's disease

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Keywords: bone fractures, dementia, dysautonomia, falls, late-stage Parkinson's disease, pain, psychosis

ABSTRACT

Late-stage Parkinson's disease is characterised by patients dependent on caregivers for their activities of daily living, even under the best levodopa benefit. Non-motor signs that overcome the well-known motor signs of Parkinson's disease dominate late-stage Parkinson's disease and few systematic data exist for the treatment of these signs. The objective of this study was to review the treatment options for Parkinson's disease dementia, psychosis, falls, bone fractures, joint and skeletal deformities, pain, orthostatic hypotension, gastrointestinal abnormalities and urological dysfunction in late-stage Parkinson's disease. The study analysed the available controlled clinical trials for the above medical conditions. When absent, data from case series and the authors' own experience was considered. Few controlled clinical trials specifically addressed late-stage Parkinson's disease as a target population. There is a need for therapeutic data on the symptoms that most afflict late-stage Parkinson's disease patients.

INTRODUCTION

The cardinal signs of Parkinson's disease are asymmetrical bradykinesia, rest tremor, rigidity and postural instability. Non-motor symptoms such as dementia, orthostatic hypotension and urinary dysfunction also occur frequently, mainly in advanced stages of the disease.[33,34]

Disability in Parkinson's disease is progressive due to the non-existence of an efficacious intervention to slow disease progression. Levodopa still remains the most effective drug for the symptomatic treatment of motor Parkinson's disease. Yet, the emergence of motor complications and the lack of benefit in non-motor symptoms limits its usefulness and adds further disability.[197,198] Although nearly 95% of patients experience motor complications in the later stages of Parkinson's disease, the non-motor symptoms appear to be the ones most contributing to disability.[56]

The first attempt to stage Parkinson's disease according to levels of impairment or disability was done in the seminal paper by Hoehn and Yahr[42] and it still holds today despite its shortcomings.[82] The Hoehn and Yahr staging does not take into account motor complications, since it was defined before the levodopa era.[42] Another classification currently used, but lacking formal definition, considers three stages in Parkinson's disease: early, stable and advanced. Under this system, patients reach the advanced stage when they start fluctuating. Therefore, the advanced stage includes early fluctuators who are moderately disabled and far advanced patients who are much more disabled.

The extreme of this spectrum, designated by late-stage Parkinson's disease, should be distinguished from the early fluctuators, because those patients have very particular needs concerning healthcare. Late-stage Parkinson's disease refers to patients who are dependent on caregivers for most of their activities of daily living, even under the best levodopa benefit (Hoehn and Yahr stage IV or V in an on period).[42] At most, these patients will still be able to stand or walk unassisted for a short distance. In addition, non-motor symptoms are usually more frequent and severe than in less advanced stages.[34,199]

This definition is based on a high level of disability, which is not contingent to the kind of impairments causing it. Yet, since it is anchored to the Hoehn and Yahr staging,[42] it implies the presence of severe motor impairments. Nonetheless, it is known that non-

motor impairments are probably the most important determinants of disability in later stages of Parkinson's disease.[56]

In future years, an increase in the prevalence of late-stage Parkinson's disease is to be expected[92,200] and this population will represent a heavy burden for their families and the healthcare system. Even so, little attention has been focused on the management of late-stage Parkinson's disease and these patients are not usually captured in clinical trials.

Considering non-motor symptoms as the main cause of disability in far advanced stages[56] and that motor complications have been recently and deeply reviewed elsewhere,[201-205] this study intends to review the available treatment options for non-motor symptoms in late-stage Parkinson's disease. The study chose those most potentially contributing to disability in this population: dementia, psychosis, falls, bone fractures, joint and skeletal deformities, pain, orthostatic hypotension, gastrointestinal abnormalities and urological dysfunction.

This review has included only data based on controlled clinical trials. An exception is made in the Expert Opinion section, where data from case series and personal experience were incorporated.

MATERIAL & METHODS

Objective: to review the evidence on the pharmacological and non-pharmacological interventions to treat non-motor symptoms in late-stage Parkinson's disease.

We selected to review those non-motor symptoms responsible for most disability of PD patients in later stages of the disease: dementia, psychosis, falls, bone fractures, joint and skeletal deformities, pain, orthostatic hypotension, gastrointestinal abnormalities and urological dysfunction. This choice was based on the results from the Sydney cohort[56-57] and our own findings reported in Chapters 1 and 2.

We searched PubMed and Cochrane Library for full-text papers of controlled clinical trials (CCT) or systematic reviews published in English, French, Spanish or Portuguese between January 1966 and December 2007, using the terms "Parkinson's disease" and "advanced", "late stage", "non motor symptoms", "dementia", "psychosis", "hallucinations", "falls", "bone fractures", "striatal hand", "striatal foot", "camptocormia", "Pisa syndrome", "frozen shoulder", "scoliosis", "pain", "orthostatic hypotension", "sialorrhea", "dysphagia", "delayed gastric emptying", "constipation", "nocturia", "urinary urgency",

"urinary frequency" and "incontinence". Reference lists of identified papers were manually searched for additional relevant studies.

In the Expert Opinion section, data from case series and personal experience were additionally incorporated.

MANAGEMENT OF LATE-STAGE PARKINSON´S DISEASE

1. Dementia

Patients with clinical suspicion of Parkinson's disease dementia should have a blood and urine work-up, a neuroimaging study (brain CT or MRI) and their medications reviewed in order to exclude treatable causes of cognitive decline.

If a work-up is negative, specific pharmacotherapy could then be tried. The best-studied drugs in Parkinson's disease dementia are the acetylcholinesterase inhibitors rivastigmine and donepezil. There are no controlled clinical trials on galantamine or memantine for Parkinson's disease dementia.[206]

1.1 Rivastigmine

A 24-week, randomised, double-blind, parallel-group, placebo-controlled trial[179] was conducted in 541 patients with mild-to-moderately severe dementia with onset at least 2 years after diagnosis of Parkinson's disease. A total of 131 patients discontinued the study prematurely, mainly due to adverse events (17.1% of patients on rivastigmine and 7.8% of patients on placebo). Improvements favoured rivastigmine for the Alzheimer's Disease Assessment Scale (ADAS – cog) ($p < 0.001$) and the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change Scale (ADCS – CGIC) ($p = 0.007$). The most frequent adverse events were nausea (29% on rivastigmine and 11.2% on placebo) ($p < 0.001$) and vomiting (16.6% on rivastigmine and 1.7% on placebo) ($p < 0.001$), while serious adverse events were similar between the groups. Rivastigmine was associated with parkinsonism exacerbation (27.3 versus 15.6%) ($p = 0.002$), mainly tremor (10.2 versus 3.9%) ($p = 0.01$), but this was not clinically relevant. An active extension study,[207] with assessments at 48 weeks, replicated the above results.

1.2 Donepezil

A randomised, double-blind, cross-over, placebo-controlled trial included 22 patients who had mild-to-moderate dementia developing ≥ 12 months after parkinsonism.[208] Donepezil had a statistically non-significant improvement for the ADAS-cog ($p = 0.18$). The scores in the Mini Mental State Examination (MMSE) ($p < 0.004$) and the Clinical Global Impression of Change ($p < 0.005$) significantly favoured donepezil compared to placebo, but the same was not true for the Mattis Dementia Rating Scale or the Brief Psychiatric Rating Scale. Adverse events occurred equally in both groups, the most frequent being worsening of psychosis and agitation.[208]

A randomised, double-blind, cross-over, placebo-controlled trial[209] enrolled 14 Parkinson's disease patients with clinical evidence of impairment in memory (an MMSE score of 16 – 26) and at least one other cognitive domain, which had an onset ≥ 12 months after parkinsonism. Donepezil resulted in a significant improvement in the scores for the MMSE ($p = 0.01$) and the Clinician's Interview Based Impression of Change plus Caregiver Input (CIBIC+) ($p = 0.03$). Three patients on donepezil withdrew due to adverse events. Parkinsonism did not aggravate with donepezil.

Another randomised, double-blind, parallel, placebo-controlled, 18-week trial[210] enrolled a mixed population of 16 Parkinson's disease patients with either a diagnosis of dementia or cognitive impairment associated with Parkinson's disease, but the authors did not state the interval between parkinsonism and cognitive impairment onset. Four patients on donepezil withdrew due to adverse events (parkinsonism aggravation = 1). Significant differences favouring donepezil were found only in the memory subscale of the Dementia Rating Scale ($p < 0.05$).

2. Psychosis

In patients presenting with psychosis, a good history is key in identifying the causes. Attention should first be drawn to any recent change in medication, to metabolic aetiologies and to infections. Brain CT or MRI may prove necessary to exclude a structural lesion. Those patients with drug-induced psychosis should be started on antipsychotics, when no further reduction of antiparkinsonian medication is possible due to motor symptoms. The choice should be among atypical neuroleptics, as classical antipsychotics severely worsen parkinsonism.

There are six marketed atypical neuroleptics: clozapine, quetiapine, risperidone, olanzapine, ziprasidone and aripiprazole. Controlled clinical trials are only available for clozapine, quetiapine and olanzapine.[206] A randomised clinical trial comparing clozapine with olanzapine was prematurely stopped because of a severe deterioration in parkinsonism with olanzapine.[211] Case series reporting on risperidone,[212-213] ziprasidone,[214-216] and aripiprazole[217-219] have described a deterioration in motor function with these drugs.

2.1 Clozapine

The Parkinson Study Group[220] randomised 60 patients with Parkinson's disease and drug-induced psychosis in a parallel-group, double-blind, 4-week trial to either placebo or low-dose clozapine. The patients had a mean age of 71 years. The psychosis outcome measures were highly statistically significant in favour of clozapine compared to placebo. Regarding safety, six drop-outs occurred: for clozapine these were due to reversible leucopaenia (one patient), myocardial infarction (one patient) and sedation (one patient), while for placebo these were due to an increase in psychosis (two patients) and pneumonia (one patient). The mean neutrophile white cell blood counts and orthostatic blood pressures were similar in both treatment arms, but there was a significantly small increase in the heart rate with clozapine. Important safety issues further arose during and after the extension phase on clozapine (n = 53) with one drop-out due to reversible leucopaenia and nine deaths due to stroke (one patient), cardiac arrest (one patient), pneumonia (two patients), bronchitis (two patients) and unknown causes (three patients). Clozapine was not associated with parkinsonism aggravation.

A randomised, parallel, placebo-controlled trial[221] consisting of a double-blind phase (4 weeks) followed by an open-label period (12 weeks) enrolled 60 patients with an MMSE score ≥ 20 who were experiencing drug-induced psychosis. Primary outcome measures significantly favoured clozapine compared to placebo. Overall, adverse events were more frequent with placebo, though somnolence and reversible neutropenia (two patients) were more frequent with clozapine. Two patients died (one sudden death and one due to aspiration pneumonia). Once again, the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores did not differ between treatments.

Other than leucopaenia, the use of clozapine has been associated with severe myocarditis and cardiomyopathy,[222-224] acute interstitial nephritis[225-226] and venous thromboembolism.[227]

2.2 Quetiapine

Thirty-one Parkinson's disease patients with drug-induced psychosis and a MMSE score > 21 were randomised to placebo or quetiapine in a double-blind, parallel-group, placebo-controlled, 12-week study.[228] The results did not show significant differences in the efficacy measures between quetiapine and placebo. Another trial that included 58 patients with drug-induced psychosis (29 patients demented) found similar results.[229]

3. Falls

Falls in late-stage Parkinson's disease may arise due to gait impairment, namely freezing of gait, postural instability, involuntary movements such as dyskinesias or foot dystonia, orthostatic hypotension or psychosis and confusion.[230] An approach to falls should begin by eliminating precipitant factors such as drug-induced psychosis, taking general measures such as removing domestic hazards or adjusting antiparkinsonian therapy.[230] This study found controlled clinical trials using falls as an outcome for the interventions outlined below.

3.1 Physiotherapy

Two systematic reviews assessed the efficacy of physiotherapy compared to placebo or no intervention in Parkinson's disease.[231,232] The authors found insufficient evidence to support or refute the use of physiotherapy in Parkinson's disease, while another systematic review,[233] using a broader definition for 'exercise therapy', concluded that these interventions are probably effective in improving functional outcomes, though this improvement is small and transitory.

Nieuwboer *et al.*[234] included 153 Parkinson's disease patients in a single-blind, randomised, cross-over trial in order to evaluate the use of a home physiotherapy programme, compared to no intervention on gait and gait-related activity (the RESCUE trial). Patients had mild-to-severe postural instability, no cognitive impairment and no unpredictable and long-lasting off periods. The primary outcome was the posture and gait score, a composite score of the gait and balance UPDRS items. Falls were a safety

measure. The results did not show a significant change in the number of falls with the use of physiotherapy, compared to no intervention (p = 0.4).

Protas *et al.*[235] conducted an 8-week, randomised, parallel, assessment-blinded, no intervention-controlled trial in order to assess the efficacy of gait and step perturbation training in reducing the number of falls and improving gait in 18 men with Parkinson's disease. The trial included patients who had a postural instability gait-predominant Parkinson's disease and experienced freezing episodes or had a history of falls and were cognitively well. The results showed a non-significant trend to fewer falls with the active intervention compared to the control group.

3.2 Occupational therapy

Two systematic reviews[231,236] found insufficient evidence to support or refute the use of occupational therapy in Parkinson's disease compared to placebo or no intervention. Instead, another systematic review[233] found that 'exercise therapy', including occupational therapy, probably had a small and transitory benefit in improving functional outcomes in Parkinson's disease.

3.3 Risedronate

Please refer to the section below on Bone Fractures.

3.4 1α-Hydroxyvitamin D3

Please refer to the section below on Bone Fractures.

4. Bone fractures

Bone fractures associated with osteoporosis and resulting from falls contribute to immobilisation, which in turn further aggravates osteoporosis and the risk of future falls.[230] Prevention of bone fractures is a result of avoiding falls (see above) and reducing osteoporosis.

4.1 Alendronate

Sato *et al.*[237] conducted a 2-year, randomised, double-blind, parallel, placebo-controlled trial in order to evaluate the efficacy and safety of the combined therapy alendronate plus vitamin D2 (ergocalciferol) in reducing the risk of hip fractures and controlling osteoporosis. The trial included 288 elderly women with Parkinson's disease and excluded patients in Hoehn and Yahr stage 5. The patients were randomised to alendronate (5 mg/day) plus ergocalciferol (1000 IU/day) or placebo plus ergocalciferol (1000 IU/day).

Withdrawals were similar between the groups. The incidence of hip fractures was four patients in the alendronate arm versus 14 patients in the placebo arm. The patients' bone mass density increased 3.1% in the alendronate group and decreased 2.8% in the placebo group ($p < 0.0001$). The adverse events with alendronate were leucopenia (one patient), oesophagitis (two patients) and diarrhoea (three patients), while three patients on placebo suffered from abdominal pain. No serious adverse events occurred.

4.2 Risedronate

Sato *et al.*[238] evaluated the efficacy and safety of risedronate in the risk of hip fractures and osteoporosis in 242 elderly men with Parkinson's disease in a 2-year, randomised, double-blind, parallel, placebo-controlled trial. Patients in Hoehn and Yahr stage 5 [6] were excluded. Patients were randomised to risedronate (2.5 mg/day) plus ergocalciferol (1000 IU/day) or placebo plus ergocalciferol (1000 IU/day). Withdrawals were similar between the groups. The incidence of hip fractures was three patients with risedronate versus nine patients with placebo. There was no significant difference in the number of falls between treatments. The patients' bone mass density increased 2.2% in the risedronate group and decreased 2.9% in the placebo group ($p < 0.0001$). The adverse events with risedronate were abdominal pain (four patients) and oesophagitis (three patients), while three patients on placebo suffered from abdominal pain or discomfort. No serious adverse events occurred.

4.3 1 α-Hydroxyvitamin D3

Sato *et al.*[239] tested the efficacy and safety of 1α-hydroxyvitamin D3 (1α(OH)D3, an active form of vitamin D) in increasing the bone mass density and in reducing the incidence of non-vertebral fractures in a double-blind, randomised, placebo-controlled trial. Patients in Hoehn and Yahr stage 5 were excluded. Eighty-six Parkinson's disease patients were randomised to either 1α(OH)D3 (1 μg/day) or placebo. After 18 months the incidence of fractures was significantly less in the active arm compared to placebo (one versus eight, respectively) ($p = 0.003$). The patients' bone mass density decreased 1.2% in the treatment group versus 6.7% in the placebo group ($p < 0.0001$). The number of falls was similar between both treatments. The authors did not report the occurrence of adverse events.

5. Joint and skeletal deformities

Several joint and skeletal deformities affect Parkinson's disease patients in later stages of the disease, namely striatal hand and foot, camptocormia (bent spine), Pisa syndrome (or pleurothotonus, a persistent flexion of the body and head to one side and axial rotation of the trunk), scoliosis and anterocollis.[240] These deformities have a differential diagnosis from lesions from rheumatoid arthritis or orthopaedic disorders. The available treatment options include antiparkinsonian drugs, botulinum toxin, baclofen and benzodiazepines, orthopaedic surgery and functional neurosurgery, although none has been tested under a controlled clinical trial protocol. Shoulder lesions, such as frozen shoulder and rotator cuff syndrome, are also experienced by late-stage Parkinson's disease patients and will mainly cause pain and limitation of joint movement (refer to section on Pain).[241,242]

6. Pain

The overall approach to pain in Parkinson's disease begins by individualising the type of pain the patient is reporting. Pain in Parkinson's disease can be categorised as either dystonic-associated or non-dystonic-associated pain, such as central, neuropathic or radicular, musculoskeletal and akathisia discomfort.[243] The choice of pharmacological and non-pharmacological interventions will depend on the above categories of pain, taking into consideration the possible coexistence of different pain syndromes in the same patient. As most pain is usually associated with a worsening of motor disability, adjustment of antiparkinsonian medication is generally the first step in controlling Parkinson's disease-associated pain.[243,244] No controlled clinical trials on the treatment of pain in Parkinson's disease were found.

7. Orthostatic hypotension

Orthostatic hypotension can result from Parkinson's disease itself and/or be secondary to dopaminergic drugs. The concomitant use of antihypertensives adds to this side effect of dopaminergic drugs. In some patients the symptoms of orthostatic hypotension are features of non-motor fluctuations and, thus, adjustment of antiparkinsonian medication will benefit these patients. The prescription of non-pharmacological treatments, such as water ingestion, raising the head of the bed and increasing salt ingestion, may be of benefit, even though evidence is lacking for the majority of these interventions.[245] The

drugs most commonly used for orthostatic hypotension are midodrine, a selective peripherally acting α-adrenergic agonist and fludocortisone, a salt-retaining mineralocorticoid.

7.1 Midodrine

A systematic review[231] identified two level-1 placebo-controlled trials in a mixed population of patients, including Parkinson's disease. In both studies, midodrine was significantly superior to placebo in increasing blood pressure, but it was associated with supine systolic hypertension and cardiovascular adverse reactions. The heterogeneity of the samples in these studies did not allow any conclusions to be drawn on the efficacy of midodrine in Parkinson's disease.

7.2 Fludocortisone, etilefrine, L-threo-3,4-dihydroxyphenylserine and yohimbine

The same systematic review[231] as above identified one trial for each of the interventions fludocortisone, etilefrine and L-threo-3,4-dihydroxyphenylserine in small Parkinson's disease samples. According to the authors, the evidence was insufficient to support their use in Parkinson's disease. The results of one trial in 17 Parkinson's disease patients showed that yohimbine is non-efficacious for treating orthostatic hypotension in Parkinson's disease.[231]

8. Gastrointestinal dysfunction

Several gastrointestinal abnormalities are experienced by late-stage Parkinson's disease patients, namely dysphagia, drooling, delayed gastric emptying and constipation, while others like small bowel mal-absorption remain to be replicated.[246,247] The management of these gastrointestinal complications is aimed at the symptoms they cause, such as dysphagia, early satiety and abdominal discomfort and the interference they cause in levodopa pharmacokinetics. Therapeutic strategies to overcome disturbed levodopa pharmacokinetics are not the aim of this review.

8.1 Dysphagia

No controlled clinical trial has assessed the efficacy of pharmacological or non-pharmacological interventions for dysphagia in Parkinson's disease.[248,249] The insertion of a nasogastric or percutaneous gastrostomy tube is a common practice in late-stage Parkinson's disease, although no data are available regarding their effect on survival or quality of life.

8.2 Sialorrhea

8.2.1 Botulinum toxin

Lagalla *et al.*[250] investigated the safety and efficacy of 50 U of botulinum toxin type A (Botox®) in the treatment of sialorrhea in 32 Parkinson's disease patients in a double-blind, randomised, parallel, placebo-controlled trial. Botulinum toxin was injected into each parotid gland without using ultrasound guidance. Patients with dysphagia requiring soft food were excluded. Botulinum toxin was associated with a statistically significant reduction in drooling frequency, familial and social disability and saliva production compared to placebo. One patient treated with botulinum toxin complained of transient dysphagia. These results have been replicated in other trials.[251-254] A small study comparing ultrasound-guided versus 'blind' injection of botulinum toxin type A in parotid glands seemed to favour ultrasound-guided injections.[255]

The efficacy and safety of botulinum toxin type B was evaluated in 16 Parkinson's disease patients in a double-blind, randomised, parallel, placebo-controlled trial.[256] Botulinum toxin or placebo was injected into each parotid gland (1000 U) and each submandibular gland (250 U) using anatomic landmarks. Patients injected with botulinum toxin reported a statistically significant improvement in drooling compared to placebo: the adverse events with botulinum toxin were mild and included a dry mouth (three patients), worsened gait (two patients), diarrhoea (one patient) and neck pain (one patient).

8.2.2 Anticholinergics

A randomised, double-blind, placebo-controlled, cross-over study in 17 Parkinson's disease patients investigated the benefit of sublingual ipratropium bromide spray.[257] Ipratropium bromide failed to show significant efficacy in the primary outcome, the weight of saliva production, compared to placebo, although it showed a mild effect in subjective measures of sialorrhea. There were no significant adverse events.

8.3 Delayed gastric emptying and constipation

8.3.1 Domperidone

One level-2 trial identified by a systematic review[231] found domperidone to be efficacious in reducing the duration of gastrointestinal emptying, in Parkinson's disease patients treated with levodopa.

8.3.2 Tegaserod

Tegaserod is an FDA-approved partial 5-HT4 agonist for the short-term treatment of women with constipation from irritable bowel syndrome. A pilot, double-blind, randomised, parallel, placebo-controlled trial evaluated the efficacy and safety of tegaserod in 15 Parkinson's disease patients with constipation.[258] The results showed a trend for decreased constipation in the active arm compared to placebo and a lack of adverse events with tegaserod.

8.3.3 Macrogol

Zangaglia *et al.*[259] tested the use of an isosmotic macrogol electrolyte solution for constipation in 57 Parkinson's disease patients, in an 8-week, randomised, double-blind, parallel, placebo-controlled study. The primary efficacy measure was the responder rate regarding constipation symptoms. Dietary habits and water ingestion were kept unchanged during the trial, in contrast to the intake of fibre. Withdrawals (n = 14) were higher with macrogol compared to placebo (31 versus 18%) and were not included in the final analysis. This analysis showed a statistically significant difference in the responder rates favouring macrogol ($p < 0.001$).

8.3.4 Cisapride

The use of cisapride has been associated with cardiac arrhythmias and sudden deaths and possibly aggravation of parkinsonism, which precludes its use in Parkinson's disease due to an unacceptable risk.[231] The US FDA has discontinued its use due to the risk of fatal arrhythmia.

9. Urological dysfunction

Urological problems in Parkinson's disease are usually associated with bladder dysfunction due to detrusor muscle hyperactivity, resulting in nocturia, urinary urgency and frequency and urge incontinence.[260] The overall approach should start by ruling out urinary tract infection and, in men, outflow obstruction by benign prostatic hyperplasia.[260] Anticholinergics are the most commonly used drugs for detrusor muscle hyperactivity, but no data based on controlled clinical trials are available regarding their use in Parkinson's disease.[231,260]

EXPERT OPINION

Late-stage Parkinson's disease stands at a phase of complex therapeutic management. Different phenomena can co-occur, namely severe motor impairment, predictable motor complications responsive to levodopa, unpredictable motor complications unresponsive to most available interventions, non-motor symptoms unresponsive to levodopa and with few efficacious alternative interventions and symptoms that endanger life such as dysphagia or, indirectly, bone fractures. Furthermore, drugs that benefit one condition (e.g., anticholinergics for urinary dysfunction) aggravate others in the same patient (dementia or psychosis). The first step in managing late-stage Parkinson's disease should be defining the therapeutic goal and respective outcome in an individual patient, knowing *a priori* this is a difficult and time- and cost-consuming task.

When facing a clinical diagnosis of Parkinson's disease dementia treatable causes should be excluded first **(Table 1)**. If a work-up is negative, specific pharmacotherapy can then be tried using the acetylcholinesterase inhibitors rivastigmine or donepezil. Up to now rivastigmine has been the best-studied drug in Parkinson's disease dementia. Its mean effect is modest and long-term data extend to just 48 weeks. More evidence is necessary to support or refute long-term use beyond that time point. One should monitor the progression of dementia to establish when no further gains from acetylcholinesterase inhibitors are likely to occur, although stopping medication may be hampered by caregivers' expectations.

Table 1. Management of Parkinson's disease dementia

Review medication (special attention to anticholinergics)
Blood and urine work-up (including thyroid function tests, vitamin B12 and folic acid level, and exclusion of infection)
Neuroimaging (CT or MRI) to exclude structural lesions such as a subdural hematoma
If work-up negative use acetylcholinesterase inhibitors rivastigmine or donepezil

Similarly, the first step in treating psychosis is to search for treatable causes **(Table 2)**.[261] Drug-induced psychosis can occur even after small changes in medication, is typically dose dependent and, thus, usually ameliorates after dose adjustment or medication withdrawal. The last added drug should be the first to be reduced or withdrawn. The usual culprits are anticholinergics, selegiline or amantadine. Next, dopamine agonists should be reduced or eliminated: if psychosis persists, catechol-O-methyl transferase (COMT) inhibitors and controlled-released levodopa are then down-titrated or excluded. If still necessary, levodopa will be reduced, with the bedtime dose being first. Of note is that tricyclic antidepressants have an anticholinergic activity.

When specific treatment is warranted, low-dose clozapine is the best choice, though blood monitoring and potential dangerous side effects hamper its use. The usual doses of clozapine are < 25 mg/day, with many patients responding to 6.25 mg/day. We are aware that many experts do not consider clozapine as first-line treatment, based on the above safety issues and practicability and alternatively favour quetiapine. Present available data do question quetiapine efficacy and raise concerns about its safety. Therefore it cannot be recommended as a first-line drug until the matter is clarified, which might mean the definition of a proper dose. There is an urgent need for an efficacious antipsychotic without the risk of serious adverse events or aggravation of parkinsonism.

Table 2. Management of psychosis

Look for recent institutionalization or home change
Blood and urine work-up to exclude infection, dehydration or metabolic imbalance
Look for falls. If appropriate, ask for neuroimaging (CT or MRI) to exclude structural lesions such as a subdural hematoma
Review recent change or adding in medication. Start by adjusting dose of most recent changed / added drug
If no recent change, adjust first anticholinergics, selegiline or amantadine
Reduce or eliminate dopamine agonists
If psychosis persists, reduce or eliminate COMT inhibitors and controlled-released levodopa formulations
If necessary, reduce levodopa (bedtime dose first)
If insufficient, begin clozapine 6.25 mg bedtime and titrate accordingly. Monitor blood and cardiac side effects

COMT: Catechol-O-methyl transferase.

Falls in late-stage Parkinson's disease may derive from postural instability, gait problems, namely freezing, involuntary movements, syncope or postural hypotension and delirium or psychotic symptoms.[262] One should first identify which factor(s) most contribute to falls in a particular patient and then target the intervention accordingly.

If iatrogenic in origin, withdrawal of cause should be attempted. Reduce on period medication when dyskinesias and/or excessive mobility are the main cause of falls.[262] Reduce dopamine agonists when facing orthostatic hypotension or syncope and introduce specific non-pharmacological and pharmacological measures for orthostatic hypotension if necessary.[262] Reduce or stop drugs inducing delirium/psychosis and evaluate hypothetic dementia.[262] If falls are mainly caused by postural instability or freezing, increasing dopaminergic drugs should be tried, chiefly if the symptoms are mostly present during off periods.[262] Balance dysfunction may partially alleviate with increasing dosage of levodopa and off period freezing usually responds to levodopa.[262] Of note is that dopamine agonists were associated with an increased frequency of

freezing.[262] Further discussion on the treatment of freezing or postural instability is beyond the topic of this review.

Evidence suggests that, at best, physical rehabilitation, as a whole, is mildly effective with a transient benefit in improving freezing, gait mobility and falls. Training targeted at falls may be worth a try in non-demented patients. We may speculate whether passive movement of joints will by itself have some impact on survival, for instance by reducing pulmonary embolism: moreover, passive movement of joints is easily performed by caregivers at no cost. Other non-pharmacological interventions might reduce falls or the morbidity from falls, namely removing domestic hazards, using proper footwear and walking aids and reducing alcohol intake: in addition, the treatment of osteoporosis will reduce the incidence of bone fractures from falls (see below).[230]

Osteoporosis in late-stage Parkinson's disease can be effectively treated using alendronate or risedronate associated with vitamin D2 or 1α-hydroxyvitamin D3, but bedridden patients will no longer benefit from these drugs. However, since these drugs take more than 1 year to have an effect and the gastric upset decreases compliance, their effectiveness might be lower than the reported efficacy.

Abnormal postures of the limbs, neck and trunk frequently complicate late-stage Parkinson's disease. A correct differential diagnosis with other clinical entities should be the first approach, such as rheumatoid arthritis, Dupuytren's contracture, de Quervain's tenosynovitis of fingers, entrapment neuropathies, cervical myelopathies or babinski sign.[240,263]

Joint deformities, such as striatal hand and foot, are unilateral as a rule and lack the typical local inflammatory signs of rheumatoid arthritis.[263] Some clinical features of striatal hand and foot overlap with other forms of dystonia and, thus, they must be differentiated from dystonia as a complication of pharmacotherapy and from those features associated with functional neurosurgery for Parkinson's disease.[263] In addition to typical striatal deformity, patients may develop severe flexion contracture of the fingers, leading to abrasion and secondary infection.[263] The rapid development of such contractures should bring attention to drug-induced reactive fibrosis in patients taking ergot dopamine agonists.[263] Striatal hand and foot may respond to levodopa and anticholinergics and some reports have described benefit with baclofen and benzodiazepines.[263] The preferred treatment is the injection of botulinum toxin in the

affected muscles, namely in the lumbricals and short adductors of the thumb, though the benefit will depend on the severity of fixed contracture.[263] In more severe cases, orthopaedic surgery can be attempted and some authors have also reported benefit with thalamotomy.[264]

A trial with levodopa or anticholinergics should be tried in patients with camptocormia or Pisa syndrome, who usually have a combination of rigidity and dystonia.[240] Patients with camptocormia and associated rectus abdominus contraction can transiently benefit from local injection of botulinum toxin.[265] In some, these postural deformities are secondary to cholinesterase inhibitors or antipsychotics, in which instances withdrawal of the offending drug is mandatory.[266]

Pain in Parkinson's disease was found to be strongly associated with motor fluctuations (adjusted odds ratio 8.6 and 95% CI = 2.1 – 35.9) (p = 0.003) and dyskinesias (adjusted odds ratio 5.1 and 95% CI = 1.6 – 15.7) (p = 0.005).[243] This association was true for dystonic- and non-dystonic-type pain, in particular musculoskeletal pain. There was also a significant correlation between the severity of pain and severity of motor complications. This same study found a lack of association between pain and medical diseases potentially associated with pain in the general population. Dystonic and non-dystonic pain were mostly reported during maximal disability (off period) and peak dose dystonia and during begin-dose or end-dose dystonia in a lesser frequency of cases. In most cases, adjustments of levodopa resulted in decreased dystonic and non-dystonic pain. Based on this and other reports,[267-268] it is suggested adjusting dopaminergic medication as the first step in treating Parkinson's disease-associated pain. Patients with severe pain during an off period may also benefit from intermittent apomorphine or botulinum toxin injections.[244]

In those patients not responding to dopaminergic drugs adjustment, an evaluation should be performed to rule out musculoskeletal and neuropathic/radicular pain, namely rotator cuff syndrome, frozen shoulder, cervical and lombar spondylosis and, less frequently, a cardio-respiratory disorder.[241] Therapy should then be directed accordingly.[244] When facing a suspicion of central or primary pain, the use of duloxetine is an option.[241] Where duloxetine is not a practical choice, a trial with tricyclics antidepressants or anti-epileptics could be tried.

Late-stage Parkinson's disease patients may also experience frozen shoulder, characterised by the insidious onset of pain, stiffness and loss of active and passive forward elevation and external rotation of shoulder.[242] The natural history is for recovery in ~ 30 months, but resolution may not be complete.[242] During the first, painful phase of disease, joint movements causing pain should be discouraged and NSAIDS can be given to alleviate pain:[242] patients benefit from intra-articular steroid injection, which is most effective when combined with physiotherapy and given early in the course of disease.[269] Physiotherapy alone is of limited value.[269,270] During the second, adhesive phase, treatment must focus on physiotherapy, and steroid injections are no longer indicated.[242]

The management of orthostatic hypotension should start by checking whether patients are taking antihypertensives or α blockers to treat prostate hyperplasia. If so, a judicious decrease in its dose should be attempted. Whenever possible, reducing the dose of agonists or, alternatively, of levodopa will be of help. An exception is made when hypotension symptoms are part of non-motor fluctuations, which implies adjustment of antiparkinsonian medication.

There is a lack of evidence to support the prescription of most non-pharmacological interventions for orthostatic hypotension in Parkinson's disease and, additionally, some of them are associated with low compliance **(Table 3)**.[245,271-273] With regard to water ingestion, it is known that the volume of ingested water influences the pressor response and that the pressor effect lasts for ~ 1h.[274,275]

When non-pharmacological interventions prove insufficient or non-compliant, pharmacotherapy should be started **(Table 4)**.[245,271-273] Although direct evidence is lacking, a first attempt with domperidone should be tried because of its additional effects on nausea, vomiting, gastroparesis and constipation. Midodrine should then be started and fludocortisone added later if necessary.[271,272] Midodrine is started at a dose of 2.5 mg/day and increased to a maximum of 10 mg, while fludrocortisone can be initiated at a dose of 0.1 mg/day and gradually increased.[199] Their use is best restricted to a dose in the early morning and early afternoon, when the symptoms are worst, taken 30 – 45 min before activity.[199,245,271-272] An important side effect is supine hypertension, especially at night and so it is critical to have supine blood pressure monitored.[199,245,271,272,276] Night-time supine hypertension worsens orthostatic hypotension because it induces pressure natriuresis, causing volume depletion.[276] In addition, it increases the risk of cardiovascular

events and end-organ damage.[276,277] When severe, night-time supine hypertension requires treatment **(Table 4)**.[271,272,276]

A recent trial, in a heterogeneous population of 58 patients with neurogenic orthostatic hypotension (including multiple system atrophy and pure autonomic failure patients), found pyridostigmine, alone or associated with midodrine, reduced orthostatic symptoms without causing supine hypertension.[278]

Table 3. Non-pharmacologic interventions for orthostatic hypotension in late-stage Parkinson`s disease

Increase water ingestion, especially in the morning. This may worsen nocturia or urinary incontinence
Liberal salt intake with foods
Avoidance of sudden head up postural change and standing still for a prolonged period of time
Avoidance of prolonged recumbence during daytime, is better to rest in a chair
Use of portable chairs during ambulation
Use of elastic abdominal binders and compression stockings (recommended to be thigh or waist high); stockings are associated with poor compliance
Soft exercise of leg and abdominal muscles, leg crossing, and avoidance of straining during micturition and defecation
Small frequent meals with reduced refined carbohydrate content, to prevent postprandial hypotension; restriction of alcohol
Avoidance of hot temperatures
During the night, lift the head of bed to diminish nocturnal sodium loss and improve OH in the morning.

Abbreviations: OH, orthostatic hypotension

Table 4. Pharmacologic interventions for orthostatic hypotension in late-stage Parkinson`s disease

Start pharmacotherapy when non-pharmacologic interventions are insufficient or non-compliant
Try domperidone first
Begin midodrine
Add fludocortisone latter, if necessary. Monitor metabolic imbalance
Instruct patients taking pressor drugs not to lye down after each dose
Avoid pressor drugs intake in the evening and water boluses at bedtime
Monitor supine blood pressure, especially at night
If nighttime supine hypertension: transdermal nitroglycerin, nifedipine, hydralazine, or clonidine. Clonidine also reduces nocturnal natriuresis

Dysphagia is a dramatic concern, putting life in danger and so requiring a pragmatic intervention, even in the face of few available data. Non-pharmacological swallowing therapy by trained personnel could be tried. Some patients may improve with dopaminergic drugs, while anticholinergics should be withdrawn, as they were reported to worsen disphagia.[279] Insertion of a percutaneous gastrostomy tube to prevent choking and aspiration pneumonia and to tranquillise patients and caregivers is advisable when dysphagia becomes severe. One should inform patients and caregivers that oral feeding is still possible after gastrostomy (for example, to eat tasty food), as this seems to be a usual concern. Patients may suffer from other oesophageal abnormalities, such as non-peristaltic swallowing, segmental spasms, oesophageal dilatation and gastro-oesophageal reflux.[280] In these instances, dopaminergic drugs seem to offer no benefit and anticholinergics may again aggravate these symptoms, as oesophageal motility depends mostly on cholinergic mechanisms.[281] Other oesophageal symptoms, such as belching, can be related to motor fluctuations and may disappear during on periods.[282]

Drooling saliva, as the result of inefficient and infrequent swallowing, is more prevalent in later stages of Parkinson's disease and during off periods.[246] In those patients whose dysphagia improves during on phases, dopaminergic drugs are a good first attempt to control drooling.[246] Otherwise, patients should be treated with botulinum toxin injections of either A or B serotype. If this is not feasible, sublingual administration of atropine ophthalmic solution could be tried before meals. This option prevents the systemic side effects and the aggravation of swallowing by oral anticholinergics. Tricyclic

antidepressants, such as amitriptyline, in low doses at bedtime are another possible approach to sialorrhea.

Gastroparesis is an issue of major concern. The factors probably associated with it are food bulk, its composition in lipids and carbohydrates, constipation and drugs such as dopamine agonists and anticholinergics.[246] Levodopa itself may aggravate gastroparesis, in cases where it remains in the stomach for too long, allowing dopa-decarboxylase to convert it to dopamine.[283] Non-pharmacological and pharmacological measures might ameliorate gastroparesis, some of them by promoting better levodopa absorption **(Table 5)**.[246,284,285]

Constipation in Parkinson's disease is mainly due to poor colonic contractions and functional outlet obstruction or both **(Table 5)**.[246,286] The functional outlet obstruction seems to result from a pelvic floor off period dystonia and usually improves with an increase in the dose of dopaminergic drugs or a local injection of botulinum toxin.[246,287]

Table 5. Non-pharmacologic & pharmacologic interventions for gastroparesis and constipation in late-stage Parkinson`s disease

Eat small regular meals; avoidance of proteins during the day. Take antiparkinsonian drugs during fasting
Diet rich in insoluble fiber
Avoidance of excessive gastric acidity
Use domperidone. Attention to possible risk of QT prolongation and ventricular tachyarrhythmia
Try macrogol or tegaserod
Management of functional outlet obstruction: advise patients to evacuate during *on* or after taking a fast-acting agonist (ex: apomorphine); increase dopaminergic drugs dose; try local injection of botulinum toxin; avoid use of laxatives

In Parkinson's disease patients with urological symptoms, an accurate diagnosis is very important in order to prevent inappropriate urologic surgery,[246] In patients complaining of detrusor overactivity symptoms, that is nocturia, urgency, frequency and urge incontinence, a urinary tract infection must be ruled out.[260] Males may complain of bladder outflow obstruction symptomatology, such as hesitancy and poor flow, due to coexistent benign prostatic hyperplasia.[246] Urgency may also be a manifestation of

obstruction, because this can cause secondary detrusor overactivity.[246, 260] Having excluded infection and obstruction, cystometry may be used to demonstrate detrusor overactivity, but pharmacotherapy can be started based solely on symptoms (**Figure 1**).[260] The postmicturition residual urine volume should then be measured by ultrasound, as the symptoms are poor predictors of the extent of incomplete emptying.[260] In cases refractory to treatment or in those with a persistently large postmicturitional residual volume an evaluation by an urologist is advisable.[260]

In candidates for prostatic surgery, a cystometry is mandatory in order to document outflow obstruction and a trial of anticholinergics is reasonable if frequency symptoms are prominent.[246] One study with subcutaneous apomorphine showed a reduction in outflow obstruction symptoms, suggesting this could be used to test the reversibility of the obstruction before prostatic surgery.[288]

Some Parkinson's disease patients also develop a hypoactive detrusor, causing difficulty in initiating micturition, incomplete bladder emptying and urinary leakage.[199] These patients could be started on α blockers, such as terazosin (1 – 5 mg at bedtime), doxazosin (1 – 8 mg at bedtime), alfuzosin (2.5 mg three times a day) or tamsulozin (0.4 – 0.8 mg in the morning).[199] However, these drugs may exacerbate orthostatic hypotension.

Declaration of Interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Figure 1. Management of detrusor overactivity

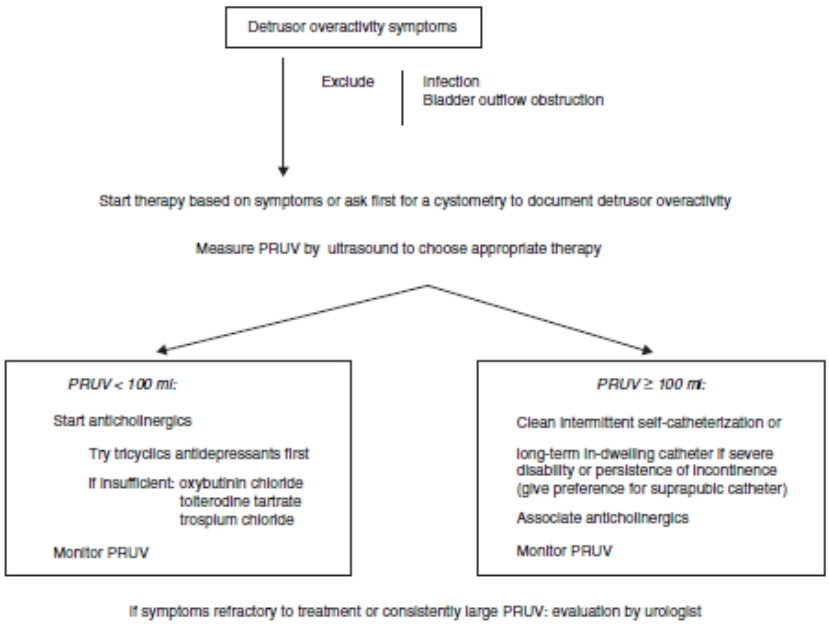

Figure 1. Management of detrusor overactivity. Start therapy based on symptoms or ask first for a cystometry to document detrusor overactivity. Measure the postmicturition residual urine volume (PRUV) by ultrasound to choose appropriate therapy. If the symptoms are refractory to treatment or there is a consistently large PRUV an evaluation by a urologist is needed.
PRUV: Postmicturition residual urine volume.

GENERAL DISCUSSION

LS-PD in the context of ageing of world population

Ageing of world population is expected to increase the prevalence of PD in future. The United Nations' Report of 2013 estimates that the global share of older people (those ≥ 60 years-old) will grow from 11.7% in 2013 to 21.1% in 2050.[289] The number of older people will more than double from 814 million in 2013 to more than 2 billion in 2050, and this will affect both developed and less developed countries.[289] Additionally, the older population is itself ageing, and the share of the "oldest old" (≥ 80 years-old) within the older population is projected to grow from 14% in 2013 to 19% in 2050, totalizing a projected figure of 392 million "oldest-old" people in 2050.[289] Taking into consideration an age-adjusted prevalence of PD of 1.8% and that ageing is the strongest risk factor for developing PD, the prevalence of PD will increase substantially worldwide by 2050.[29,290] Likewise, an increase in life expectancy and better clinical management of PD is likely to increase the number of patients with a more prolonged disease course.[92,291] As a longer duration of PD is associated with a higher frequency of motor symptoms and NMS resistant to L-dopa, the number of patients in LS-PD is also projected to increase substantially in the future.[291]

This increase in the frequency of LS-PD will carry a higher burden of disease for patients, caregivers, and the healthcare and social security systems.[291] Regarding the burden of patients, this is mostly driven from disability due to L-dopa resistant symptoms, for which we lack efficacious therapeutic interventions in the majority of the cases.[41,56,57,154] Similarly, caregivers' burden correlates with disease progression and weekly hours of caregiving.[141,143,144] Its major determinants are the symptoms that dominate LS-PD, behavioural and cognitive dysfunction, postural instability and falls.[141,143,144] High burden of patients and caregivers impacts tremendously on society, at the level of the healthcare and social security systems, and having economic costs.[291-293] Briefly, this is reflected in loss of employment and productivity, increase in outpatient and inpatient care, prescription costs and frequency of institutionalization.[291-293] In fact, neurological disorders constitute 6.3% of the global burden of disease according to a WHO report, pinpointing neurological disorders as one major threat to public health.[294] Although much less than the global burden from stroke or Alzheimer's disease, PD contributes significantly to the loss of disability-adjusted life years (DALYs), that is, the number of

years expected to be lived in full health.[294] Despite lacking specific data, we may speculate that LS-PD contributes even more to loss of DALYs than less advanced stages of PD. At an individual healthcare level, doctors and allied health professionals treating PD will face more frequently patients in late-stage, for whom they lack knowledge on the symptoms that most impact on their disability and which need to be prioritized. Patients in this stage are at risk of institutionalization and healthcare professionals working in nursery homes, who are not necessarily neurologists, will care more frequently for these patients. A recent study in Netherlands found that PD patients in nursery homes were severely disabled but almost half were considered to be undertreated according to a movement disorders neurologist, probably due to lack of knowledge of the specific needs of these patients.[295]

Overall, this asks for a rational allocation of effective health and social security resources that cover patients' and caregivers' needs, but for which planning is crucial the existence of evidence on the health needs of LS-PD patients. That data is only partly reported nowadays. We think we have made a contribution to this body of evidence by specifically studying this emerging group of PD patients. We have covered the clinical manifestations of LS-PD patients, measured their handicap and the factors most contributing to handicap and perceived health status (HS), identified the medication use and the interventions from allied health professionals that these patients are using, and the overall healthcare they get, and we explored the burden of the carers of these patients and how they are affected by their relatives' disease and handicap. Finally, we reviewed the available treatment options for the management of NMS, which are a major burden for these patients.

Clinical features and handicap of LS-PD patients and burden of their carers

We found that LS-PD patients still attending movement disorders clinics have long disease duration and a relatively young onset of PD. This contrasts with the reports of Weerkamp *et al*[295,296] and Makoutonina *et al*[297] on severely disabled parkinsonian patients living in nursery homes who were older, had a mean age at disease onset of 68 years and a mean PD duration of 10-12.7 years. Several reasons might explain this difference: almost half the patients (73 PD Dutch patients mostly in HY stage 4 or 5) included in the Weerkamp *et*

al study[295,296] were considered to be in *off* state during most of the day and undertreated (25% were taking < 400 mg of L-dopa daily), so that one may speculate that part of them would no more be classified as HY stage 4 or 5 once they got the right treatment; secondly, PD starting at older age is a risk factor for a more severe disease course, which could additionally explain why these patients were institutionalized after only 8-9 years of disease;[298,299] finally, the diagnosis of the patients (49 Australians with parkinsonism) included in the Makoutonina *et al* study[297] could not be confirmed by the authors, so that cases of atypical, vascular or drug-induced parkinsonism may have been included. In addition and similarly to Weerkamp *et al* study, the patients included by Makoutonina *et al*[297] were also treated with very low doses of L-dopa (mean 390 mg). On the other hand, our results also contrast with the reports of the long-term outcome of PD patients submitted to DBS, who also have very long disease duration as did our patients.[76-78,88,89,300-302] After 8-11 years of DBS, PD duration was longer (18-26 years) but patients were younger (<70 years) and had a younger age at disease onset (39.6-49 years) than ours. Even though having a longer disease duration, DBS patients had a better motor (UPDRS motor score 23.4-35) and ADL score (UPDRS part II ADL score 17.8-20), a better speech score (UPDRS mean speech item score 1.9-2.7) and less dementia (22.7-46%), but worse rigidity (UPDRS mean rigidity item score 3.4-5), than our patients.[76-78, 88,89,300-302]

Our LS-PD patients are severely disabled from motor and non-motor symptoms. They have a symmetric akinetic parkinsonism with negligible rigidity and postural tremor, associated with severe postural instability, freezing of gait and falls, and prominent dysarthria and dysphagia. Interestingly, this motor syndrome is distinctly different from the classical motor phenotype of PD. Motor fluctuations and dyskinesias are frequent but not disabling, possibly in accordance with patients' perception that L-dopa is still effective in partially relieving motor symptoms including tremor, though not potent enough to put patients in a good *on* state. Neuropsychiatric and dysautonomic symptoms are universal in these patients, and NMS fluctuate with L-dopa in two-thirds of the cases. Dementia is not inexorable in late stages of PD, as only half were demented, and the risk of dementia is higher in akinetic patients compared to tremor-dominant PD, as it is well established.[61,303-305] The partial loss of benefit from L-dopa may be apparent owing to the use of lower than needed doses of antiparkinsonian drugs due to the frequent occurrence

of neuropsychiatric symptoms, or because of disease progression with increasing non-dopaminergic involvement. Equally, the low doses of L-dopa found by Weerkamp *et al*[295,296] may also be explained as a strategy to avoid side effects. We think there is a need to accurately assess the response of these patients to L-dopa. The disability of LS-PD patients may be also due to frequent co-morbidity and past medical diseases, although this was not apparent in our regression model. Despite severe disability and co-morbidity, they make low use of health resources such as allied health professionals, which is increasingly recommended.[306,307] In contrast, almost all receive unpaid care, and the majority lives at their house. These unpaid caregivers spend much time with patients and report a high burden that is strongly determined by patients' handicap.

We found that LS-PD patients are highly handicapped, using the London Handicap Scale. The domain of handicapped most affected is Orientation, reflecting the high frequency of cognitive impairment in these patients. Accordingly, handicap is mostly driven by the presence of dementia, behavioural complaints and the severity of non-dopaminergic motor features. Interestingly, symptoms causing greatest impact on perceived HS of our patients (falls, gait unsteadiness, urinary dysfunction and sweats) do not fully overlap those associated with greater handicap, suggesting that handicap and perceived HS are similar but distinct measures of health states.[101,308] In fact, perceived HS refers to perceived health in terms of physical and mental symptoms, social conditions or functions, and represents the impact of health on one's ability to perform a variety of physical, emotional and social activities.[101] Our study also found that patients with disabling L-dopa-induced motor complications (MC) have a moderate-to-severe handicap, although less than LS-PD patients. Moreover, the most affected domains of handicap in patients with MC are Physical Independence and Social Integration, whereas disability in ADL and dyskinesias are its major determinants. Overall, this data strongly suggest that LS-PD is distinctly different from advanced stage PD.

We could measure handicap in LS-PD and advanced stage PD patients using the LHS, which was easily completed by patients and caregivers. In our study, we have explored for the first time handicap as a patient-centred outcome (PCO) measure in PD. The inclusion of PCO in PD research is increasingly important. Data on the health burden of PD from patients' perspective are essential to understand the impact of disease in patients, to complement objective measures and to assess the effectiveness of therapeutic

interventions. The most commonly used PCO measures in PD research are the perceived HS, interference in ADL, the QoL and the health-related QoL (HRQoL).[101,123,309,310] Handicap is a rarely used PCO in PD, although widely used in other chronic neurological or non-neurological diseases, such as stroke sequelae.[125,126,129,132,153,311-320] Although the WHO recently renamed the term *handicap* for *participation restriction,* the concept of handicap still holds true for clinical research.[135-137] During the revision process led by the WHO, it was found a strong transcultural agreement on 6 domains of participation that can be potentially affected by health states,[135-137] which, importantly, correspond to the 6 usual dimensions of handicap. In contrast to handicap, QoL represents the internal experience of patients regarding the way they perceive and react to their health status and other non-medical aspects of their life, in the context of the culture and value systems in which the individual lives and in relation to her/his goals, expectations, standards and concerns.[101,321,322] Although intimately related to the concept of (HR)QoL, handicap is more objective and more easily understandable to patients and caregivers, and allows the latter to answer the questionnaires in case patients are unable to do so owing to dementia or severe akinesia and dysarthria.[125,129] Furthermore, comparison between populations of different origins is possible because there is good transcultural agreement on the construct of handicap.[133,323] Overall, handicap might prove more understandable to patients and caregivers than (HR)QoL and a harder PCO measure of the impact of disease in the functioning of an individual. Our study provided for the first time data on the values of the LHS for advanced and late stage PD patients, which can be used as reference for future studies. The scale was easily completed by patients and caregivers of these 2 populations of PD, and it was brief to complete. In future, it would be important to assess the use of the LHS in earlier stages of PD and to evaluate how the scale behaves after an intervention, namely DBS.

LS-PD is a distinct sub-group of advanced stage PD: proposal of a definition

Our choice of the HY scale to define LS-PD patients resulted in the inclusion of very disabled patients due to motor and non-motor symptoms as was our intention, despite the limitations of the HY scale.[82] Selecting our target population of LS-PD patients according to the presence of disabling MC, the most widely accepted definition for

advanced stage of PD, would have left out from the sample the most disabled PD patients and, additionally, would not capture very disabled patients who do not manifest MC at all. Paradoxically, the very disabled LS-PD patients that we included in the study are nowadays classified under the generic umbrella of *advanced stage* PD, although their phenotype vary considerably from the classic definition of patients in *advanced stage*. Indeed, the clinical features of patients with disabling MC selected to DBS that we report in Chapter 3 are very different from our LS-PD population. We think there is now enough data to conclude that LS-PD is a distinct sub-group of advanced stage PD. Besides, the emergence in future of LS-PD as a frequent and very disabling phenotype in the progression of PD will probably determine a change in the way we conceive today the natural history of PD.

We propose the term *late-stage* to describe patients who are highly dependent on others in ADL, owing to L-dopa-resistant motor symptoms or NMS, at the best of L-dopa effect. Even though we have initially chosen the HY scale to define *late-stage* patients, we now propose to use the S&E scale[95] to define *late-stage* patients, based on our results. The usage of the HY scale implies defining *late-stage* anchored in motor disability. Instead, the S&E scale is a tool developed to measure PD patients' perceived functional independence.[95] In our study, the mean S&E score of LS-PD patients was 30% in *on* and 23% in *off* state, respectively. We think that a higher cut-off score would still allow to include very disabled patients due to motor or non-motor symptoms resistant to L-dopa. As a result, our proposed operational definition of *late-stage* PD is a score on the S&E scale of less than 50% during *on* period. A score of 50% corresponds with the patient requiring help with half of the chores and experiencing difficulty with all activities, while a score of 40% implies the patient being highly dependent on carers, able to assist with all chores, but unable to complete most tasks alone. Finally, albeit we think that the S&E scale and a 50% threshold are suitable to define LS-PD, discussion and further validation is still required.

Treatment of NMS in LS-PD

Since LS-PD patients are mostly disabled from axial motor and non-motor symptoms, the treatment of these symptoms is of paramount importance. In this regard, we reviewed the evidence on the pharmacological and non-pharmacological interventions to treat

these symptoms, using the principles of evidence-based medicine. Target symptoms to review were those responsible for most disability of PD patients in the later stages of disease and more specific of these later stages, based on the results from the Sydney cohort and our own study.[56,57] This justifies why depression and anxiety were not reviewed: although frequent and disabling in later stages of PD, they are also very frequent in earlier stages of disease. At the time of the review, we considered "falls" a NMS which is something we would not do nowadays, as is manifest in this manuscript and other recent publications from our group.[324-325] In fact, we had recently the opportunity to work in a systematic review of the treatment for the motor and non-motor symptoms of PD in which "falls" were classified among the motor symptoms of PD.[41,154]

For the review, we selected controlled clinical trials (CCT) addressing the chosen target symptoms of LS-PD. However, these CCT enrolled PD patients who did not necessarily satisfied criteria for late-stage and we explicitly did not restrict our review to CCT recruiting late-stage patients only. This implies that the results of the review apply to PD patients in general but we do not know the effectiveness and safety of the covered interventions specifically in LS-PD patients.

For many symptoms we did not find any CCT, and in other cases the quality of the trials is poor, indicating that there are unmet needs in the treatment of the symptoms affecting this population of PD patients. Furthermore, few trials included patients in late-stage and in many that information is not available in the report. As expected, the therapeutic interventions did not include L-dopa, suggesting that mostly these NMS are mediated through non-dopaminergic pathways.

Implications for clinical practice

This new and emerging phenotype of LS-PD is distinct from the classical advanced stage patients, and our study made possible to detail its clinical features, medication use, determinants of handicap and available treatment options tested in CCT. LSDP patients and their caregivers will be a clinical challenge to treating physicians, whether neurologists, geriatricians or general practioners, and allied health professionals. This health personnel and patients´ caregivers will require specialist training to manage these patients.

Health professionals should be proactive in asking patients and caregivers about the symptoms which we now know most contribute to their handicap. Clinical assessment and therapeutic interventions should focus on such problems as falls and postural instability, urinary dysfunction, freezing, bradykinesia, dysarthria and choking, dementia, psychosis, excessive daytime sleepiness, apathy, depression and anxiety. However, rigorous ascertainment of some of these symptoms is particularly difficult in this population, owing to severe dysarthria, dementia and daytime somnolence. Treatment for MC should be less of a priority.

Adequate management of this population of patients and their caregivers is complex and requires a multidisciplinary approach. Both health and social interventions will probably be necessary to improve the health state and reduce the handicap of these individuals, and these interventions must be cost-effective. Therapeutic interventions should be pharmacological and non-pharmacological. Unfortunately, effective treatments are lacking for many of these L-dopa-resistant symptoms, as shown by our study and more recent work.[41,154,326] Pharmacological management is further complicated by a high frequency of adverse effects in these patients, and so management strategies should aim for regimen simplification.

Implications for research

Basic research regarding the pathogenesis and neuropathology of L-dopa-unresponsive symptoms is fundamental to achieve new understanding that will allow research of innovative molecules to treat these disabling symptoms.[327] This research should focus on non-dopaminergic pathways and extra-nigral structures.[1,2,191,328]

There is plenty to do regarding clinical research in LS-PD. Longitudinal data on the motor and non-motor progression of LS-PD patients is valuable in order to estimate, even though indirectly, the rate of neurodegeneration at this late stage which is known to differ from that in earlier stages.[168] LS-PD is a good clinical model to identify the disability milestones that cause most disability and predict mortality, highlighting the symptoms that should be targeted for drug development at earlier stages of PD.[105,188] Studies assessing the clinimetrics of scales for PD have, as a rule, included few late stage patients so it is lacking robust data on the behaviour of most scales in this population. In fact, many of the available scales may even not be adequate to assess these very advanced

patients, and adaptations of these scales or even new tools may be needed. Other research techniques such as qualitative research may be of value addressing the multiple problems of these patients and carers. Missing is still a precise evaluation of the response of the motor and non-motor symptoms of these patients to L-dopa, to disclose whether the reported loss of benefit from L-dopa is only apparent due to the use of low doses because of side effects or the consequence of widespread disease progression.[295,296] Finally, new CCT testing therapeutic interventions or management strategies in LS-PD are urgently needed.[307,329]

ABBREVIATIONS

* ADL	Activities of daily living
* BDI	The Beck Depression Inventory
* CI	Confidence interval
* COMT inhibitors	Catechol-O-methyl transferase inhibitors
* CT	Computed tomography
* DALYs	Disability-adjusted life years
* DBS	Deep brain stimulation
* (HR)QoL	Health-related Quality of life
* HS	Health status
* HY	Hoehn and Yahr
* L-dopa	Levodopa
* LEDD	Levodopa equivalent daily dose
* LHS	London Handicap Scale
* LS-PD	Late-stage PD
* mAIMS	modified Abnormal Involuntary Movement Scale
* MC	Motor complications
* MDS-UPDRS	Movement Disorders Society- Unified Parkinson's disease Rating Scale
* MMSE	Mini Mental State Examination
* MRI	Magnetic resonance imaging
* NA	Not applicable or not available
* NMS	Non-motor symptoms
* PCO	Patient-centred outcome
* PD	Parkinson`s disease
* QoL	Quality of life
* SD	Standard deviation
* S&E	Schwab & England Scale
* SN	Substantia nigra
* SNpc	Substantia nigra pars compacta
* UPDRS	Unified Parkinson`s Disease Rating Scale

* WHO World Health Organization

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ORIGINAL COMMUNICATION

Late-stage Parkinson's disease: the Barcelona and Lisbon cohort

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Abstract Studies of late stages of Parkinson's disease (LS-PD) are limited. To provide an adequate health plan for patients in these most advanced stages, accurate information on their clinical condition is necessary. We characterize clinical features and medication use of LS-PD. A cross-sectional study of LS-PD stage 4 or 5 of Hoehn and Yahr during *on* states is presented in this paper. Demographics, clinical features and medication data were obtained using a structured questionnaire and physical examination. Patients were asked to grade the perceived impact of symptoms on their health status. Fifty patients (mean age 74.1 years and mean disease duration 17.9 years) were studied. Severe akinetic symmetric parkinsonism was present in most, with negligible rigidity and tremor, and most patients were wheelchair-bound. Severe postural instability and freezing of gait, causing frequent falls and fractures, and prominent dysarthria and dysphagia dominated the motor syndrome. Levodopa remained effective in most patients in relieving motor symptoms including tremor. Motor fluctuations and dyskinesias were present in 78 and 62% of patients, respectively, but were not perceived as disabling. All had neuropsychiatric and dysautonomic symptoms. Visual hallucinations were present in 44%, depression in 62% and dementia in 50%. Lack of tremor ($p < 0.01$) and absence of depression ($p < 0.01$) were independently associated with dementia ($R^2 = 45\%$). Symptoms causing greatest impact on perceived health status were falls, gait unsteadiness, urinary dysfunction and sweats. Motor and non-motor non-levodopa responsive problems were frequent and the main cause of disability. Fluctuations and dyskinesias were frequent though not disabling. Dementia is not unavoidable in these very late stages.

Keywords Parkinson's disease · Motor fluctuations · Late-stage · Dementia · Disability

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Introduction

Parkinson's disease (PD) is a chronic disease with progressive disability. The clinical characteristics of late-stage PD (LS-PD), when disability is most severe, have been only partially described. In the pre-levodopa era, reporting on the clinical features of 100 parkinsonian patients, Martin et al. [1] found that patients in later Hoehn and Yahr (H&Y) stages had frequent and severe cognitive decline besides severe motor impairment. In recent times, after the introduction of therapies such as levodopa or deep brain stimulation, cross-sectional studies have shown worsening of sleep problems, dysautonomia and cognition with advancing disease [2, 3]. The longitudinal studies by Hely et al. [4, 5], describe patients in late-stage PD with common but not disabling dyskinesias and on–off fluctuations, with dementia and dependency on carers eventually occurring in most, whose major disability relates to motor and non-motor symptoms not improved by levodopa.

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Better general healthcare, and better understanding of complications and clinical management of PD, is likely to increase the prevalence of LS-PD in the future [6]. These very advanced patients will represent an important burden for families and the healthcare system. Since knowledge of the health needs of these disabled patients is crucial to plan effective health resources that cover patients' and caregivers' needs, we thought to study the clinical features and handicap of LS-PD patients attending two tertiary centers, selected on the basis of motor disability. We report in this paper the results concerning the clinical features.

Patients and methods

Study participants

PD patients who attend the movement disorders clinics of two tertiary university hospitals were studied. PD was diagnosed according to the UK Parkinson's Disease Society Brain Bank Criteria [7]. Patients in stage 4 or 5 of Hoehn and Yahr in *on* states were included (stage 4 = patients with severe disability but still able to walk or stand unassisted; stage 5 = wheelchair bound or bedridden unless aided) [8]. Patients with a diagnosis of parkinsonism other than idiopathic Parkinson's disease were excluded. The study was approved by the local ethical committees. Informed consent was obtained from the patient or, if dementia was present, the caregiver.

Study design

This was a cross-sectional study performed in two tertiary university hospitals, one in Barcelona, Spain (Hospital Clínic Universitari) and other in Lisbon, Portugal (Hospital Santa Maria). Consecutive patients were recruited from the outpatient clinics during a 24-month period. Data were collected by interviewing patients or, if the patient was not competent, their caregivers. In those infrequent instances when only the caregiver was present in the outpatient clinic, the patient was later evaluated at home by one of the authors (MC).

Patients evaluation

Data on demographics, clinical manifestations and disease management were obtained using a structured questionnaire and a physical examination form. Medical charts were reviewed when needed.

Severity of parkinsonism and activities of daily living (ADL) were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Schwab and England Scale (S&E) [9], respectively. Part III (motor) of UPDRS was assessed during *on* periods. Parkinsonism was considered asymmetric when right–left differences in tremor, bradykinesia and rigidity were $\geq$5 points on the UPDRS items 20–23 and 25–26 [10].

Levodopa-induced motor and non-motor complications were assessed with part IV of UPDRS, the structured questionnaire and the neurological examination. We established whether they were present at the time of evaluation, had been present in the past but were currently absent, or had never been present. Patients were asked to rate current dyskinesias as either troublesome or not troublesome.

Non-motor symptoms [11] were assessed in three domains: behavioral and cognition; dysautonomia; and other (sleep, fatigue, pain, paresthesias, anorexia, drooling and kyphoscoliosis). Dementia and depression were diagnosed according to the DSM-IV definitions [12]. Cognition and mood were rated using the Mini Mental State Examination (MMSE) [13] and the Beck Depression Inventory (BDI) [14], respectively. Orthostatic hypotension was defined as a decrease in systolic pressure $\geq$20 mmHg or/and in diastolic pressure $\geq$10 mmHg, within 3 min of standing. Patients were asked to grade the impact caused by symptoms on their perceived health status (0 = none; 4 = extreme) [11, 15].

We obtained data on current medication use and side effects, and patients were asked to judge the response of symptoms to levodopa (improves; worsens; no response).

Statistical analysis

The software program SPSS 12.0 (SPSS, Chicago, IL) was used for database and statistical analysis. We performed a descriptive analysis for each variable. Comparison of cohorts from Lisbon and Barcelona was done, using independent samples t test and Mann–Whitney U test for comparison of continuous variables, and Pearson χ^2 test and Fisher Exact test for differences in proportions. Concerning the impact caused by symptoms on patients' perceived health status, we calculated the median value (0 = none; 4 = extreme) for each symptom reported by patients. Variables associated with dementia (dependent variable) at a significance level of $p \leq 0.1$ were included in a multivariate logistic regression analysis, using likelihood ratio forward stepping. Two-tailed p values <0.05 were considered significant.

Results

Fifty patients were included (Barcelona 28, Lisbon 22). Demographic data are shown on Table 1. Disease characteristics were comparable in the two groups of patients, except for medication (see below).

Table 1 Demographic characteristics and Hoehn and Yahr stage score in late-stage PD patients

Characteristic	PD patients
n	50
Age (years) (mean (SD))	74.1 (7.0)
Women (*n* (%))	27 (54)
Age at disease onset (years) (mean (SD))	56.2 (10.4)
Duration of disease (years) (mean (SD))	17.94 (6.3)
Education (years) (mean (SD))	7.6 (4.7)
Hoehn and Yahr stage[a] (*n* (%))	
4	30 (60)
5	20 (40)

PD Parkinson's disease

[a] Scored during *on* period

Clinical manifestations

Motor symptoms

As expected, slowness of movement occurred in all patients, and was severe in most (Table 2). Arm rest tremor was present in eight (16%) (severe in one), and also affected lower limbs in two. Mild postural tremor was observed in 25 (50%) patients, including all the patients with rest tremor. Limb rigidity was detected in 32 patients (64%), and was mild in most. All patients had postural instability in accordance with selection criteria for the study.

Freezing of gait was reported by 31 patients (62%), and in 15 it was frequent and a cause of falls. Falls occurred in 25 (50%), and in 14 cases they occurred daily. Of those 25 patients, 20 were H&Y stage 4 and five were H&Y stage 5. Forty-eight (96%) reported problems with speech, which was difficult to understand or unintelligible in 26. Dysphagia was reported by 34 (68%). Ten experienced occasional choking, thirteen required soft food, seven had a nasogastric tube, and in five feeding was through a gastrostomy.

At the time of evaluation, 72% of patients perceived that levodopa improved mobility, and 90% that it improved tremor. 73% of patients thought levodopa had no effect on unsteadiness, and 16% had the perception levodopa worsened falls. Still, 52% thought it improved freezing. Though 37% of patients reported some benefit from levodopa on speech, dysphagia did not improve among 82%.

Levodopa-induced motor complications

Levodopa-induced motor complications were present in 39 patients (78%) at the time of the study (motor fluctuations in 39; dyskinesias in 31) (Table 3). They had occurred in an additional eight patients (motor fluctuations in eight; dyskinesias in two) at some point during the disease course but had later remitted. Wearing-off occurred in all 39 patients. O*ffs* occupied <25% of the day in 19, 26–50% of the day in eight, and >75% of the day in seven patients. The mean difference in UPDRS ADL score ($n = 39$) between *on* and *off* was statistically significant ($p < 0.05$), and the same was found for the Schwab and England Scale ($n = 39$) ($p < 0.01$) (Table 4).

Dyskinesias were troublesome in 13 (26%), but in only four they were severely disabling (UPDRS score 3 or 4). Dyskinesias occupied <25% of the day in 17, and >75% of the day in four patients.

Table 2 Motor symptoms in late-stage PD patients

	PD patients ($n = 50$)
Asymmetric disease (*n* (%))	16 (32)
Slowness of movement (*n* (%))	50 (100)
UPDRS limb bradykinesia items, median[a]	3
Postural instability (*n* (%))	50 (100)
Dysarthria (*n* (%))	48 (96)
UPDRS speech, median[a]	3
Neck rigidity (*n* (%))	39 (78)
UPDRS neck rigidity, median[a]	2
Dysphagia (*n* (%))	34 (68)
UPDRS swallowing, median[a]	2
Limb rigidity (*n* (%))	32 (64)
UPDRS limb rigidity items, median[a]	1
Freezing (*n* (%))	31 (62)
Falls (*n* (%))	25 (50)
Tremor (*n* (%))	25 (50)
Rest tremor (*n* (%))	8 (16)
Asymmetric rest tremor (n (%))	7 (14)
Postural tremor (n (%))	25 (50)
Head tremor (n (%))	2 (4)
UPDRS tremor items, median[a]	0
Fixed dystonia (*n* (%))	24 (48)
Bone fractures in the previous 5 years (*n* (%))	10 (20)
Need for a wheelchair (*n* (%))	39 (78)
Gastrostomy (*n* (%))	5 (10)
UPDRS motor *on* (mean (SD))[a]	49.18 (13.0)

UPDRS Unified Parkinson's Disease Rating Scale, *PD* Parkinson's disease

[a] Higher numbers indicate a greater severity of impairment

Cognition, mood and behavior

Neuropsychiatric symptoms were present at the time of examination in all patients (Table 5). Visual hallucinations and delusions had occurred in an additional 22 and nine patients, respectively, at some point during the disease course but had later remitted.

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Table 3 Levodopa-induced complications in late-stage PD patients at the time of study assessment

	PD patients ($n = 50$)
L-dopa-induced motor complications (*n* (%))	39 (78)
Wearing-off (*n* (%))	39 (78)
Off duration >75% of the day (*n* (%))	7 (14)
No *on* response (*n* (%))	17 (34)
Morning dystonia (*n* (%))	11 (22)
Off dystonia (*n* (%))	9 (18)
Delayed *on* response (*n* (%))	7 (14)
Morning akinesia (*n* (%))	5 (10)
On/off phenomena (*n* (%))	2 (4)
Dyskinesia (*n* (%))	31 (62)
Peak-dose (*n* (%))	15 (30)
Diphasic (*n* (%))	9 (18)
Square-wave (*n* (%))	7 (14)
Troublesome dyskinesias (*n* (%))	13 (26)
Dyskinesia duration >75% of the day (*n* (%))	4 (8)
Severe or complete disabling dyskinesia (*n* (%))	4 (8)
L-dopa-induced non-motor fluctuations (*n* (%))	33 (66)
Neuropsychiatric (*n* (%))	24 (48)
Dysautonomic (*n* (%))	11 (22)
Sensory (*n* (%))	8 (16)
UPDRS part IV (mean (SD))[a]	5.3 (3.5)

UPDRS part IV treatment complications component of Unified Parkinson's Disease Rating Scale, *PD* Parkinson's disease, *L-dopa* levodopa

[a] Higher numbers indicate a greater severity of impairment

Table 4 Performance in the activities of daily living of late-stage PD patients

UPDRS ADL (mean (SD))[a]		
On	28.2 (6.3)	$p < 0.05$[c]
Off	29.6 (5.8)	
S&E (mean (SD))[b]		
On	31.0 (15.7)	$p < 0.01$[c]
Off	23.2 (14.2)	

UPDRS Unified Parkinson's Disease Rating Scale, *ADL* activities of daily living, *S&E* Schwab and England scale

[a] Higher numbers indicate a greater impairment

[b] Higher numbers indicate more independency in the activities of daily living

[c] Not considered clinical relevant

Thirty-one patients (62%) were depressed. Nineteen depressed patients also reported symptoms suggestive of apathy.

Dementia was present in 25 (50%) patients. Mean MMSE score in 22 demented patients was 11.8 (SD ± 6.5), while it was 23.5 (SD ± 4.5) in the non-demented. The MMSE cutoff score is adjusted to literacy in Spain and Portugal and the above value of 23.5 points does not configure dementia in those populations. Thirteen demented patients reported visual hallucinations and 10 reported delusions. Variables (univariable analysis) that were statistically significantly associated with the presence of dementia were lack of tremor ($p < 0.01$), absence of depression ($p < 0.01$), symptoms suggestive of apathy ($p < 0.01$), daytime somnolence ($p < 0.05$), absence of irritability ($p < 0.05$), less consumption of antiparkinsonian drugs ($p < 0.01$), and worse scores on UPDRS ADL part ($p < 0.01$), UPDRS part IV ($p < 0.05$) and S&E scale ($p < 0.05$). In a multivariable logistic regression analysis, lack of tremor ($p < 0.01$) and absence of depression ($p < 0.01$) remained independently associated with dementia. This model could predict the presence of dementia in 72% of the cases and explained its occurrence in 45% (Nagelkerke R Square).

Neuropsychiatric symptoms severity changed with levodopa intake in 48% of patients (Table 3). Improvement was reported in sadness (13.5% of patients), apathy (32%), slowness of thinking (44%), anxiety (25%), and irritability (37%) after a levodopa dose. Worsening of anxiety and irritability was reported by a small proportion of patients (8 and 5%, respectively). Aggressive behavior was mostly (75%) unaffected by levodopa.

Dysautonomic complications

Dysautonomic symptoms occurred in 48 patients (96%) (Table 5). We measured arterial blood pressure in 18 and documented orthostatic hypotension in three.

Pain, sleep and other symptoms

Sleep disturbances were very frequent and sensory symptoms were reported by 19 patients (38%) (Table 5).

Impact of symptoms on perceived health status

Symptoms causing an extreme or severe impact on patients' perceived health status were in most instances motor and non-motor symptoms that do not respond to levodopa (Table 6).

Medication

At the time of the study, 49 patients (98%) were taking levodopa, as monotherapy ($n = 18$) or in combination with other antiparkinsonian drugs ($n = 31$) (Table 7). Mean daily doses of ropinirole was 6 ± 3.6 mg/day; of pergolide 1.8 ± 1.2 mg/day; of pramipexole 0.68 ± 0.42 mg/day; of cabergoline 2.5 ± 2.4 mg/day; of bromocriptine 10.7 ± 5.1 mg/day and of piribedil 150 ± 0.0 mg/day. Statistically

Table 5 Non-motor complications in late-stage PD patients

	PD patients ($n = 50$)
Cognition, mood and behavior (n (%))	50 (100)
Depression (n (%))	31 (62)
BDI in 15 testable depressed patients (mean (SD))	16.8 (5.29)
Symptoms suggestive of apathy (n (%))	28 (56)
Slowness of thinking (n (%))	25 (50)
Anxiety (n (%))	25 (50)
Dementia (n (%))	25 (50)
MMSE in 44 testable patients (demented and non-demented) (mean (SD))	17.7 (8.1)
MMSE in 22 demented patients (mean (SD))	11.8 (6.5)
MMSE in 22 non-demented patients (mean (SD))	23.5 (4.5)
Visual hallucinations (n (%))	22 (44)
Irritability (n (%))	20 (40)
Delusions (n (%))	16 (32)
Aggressive behavior (n (%))	8 (16)
UPDRS part I (mean (SD))[a]	6.4 (3.9)
Dysautonomic complications (n (%))	48 (96)
Constipation (n (%))	41 (82)
Urinary dysfunction (incontinence, urgency or retention) (n (%))	32 (64)
Hyperhidrosis (n (%))	18 (36)
Sweats (n (%))	18 (36)
Orthostatism (item 42 of UPDRS) (n (%))	13 (26)
Dyspnea (n (%))	7 (14)
Syncope (n (%))	4 (8)
Pain, Sleep and other symptoms	–
Night sleep problems (n (%))	30 (60)
Diurnal somnolence (n (%))	18 (36)
Pain (n (%))	12 (24)
Anorexia (n (%))	11 (22)
Paresthesias (n (%))	10 (20)
Sleep attacks (n (%))	5 (10)
Weight loss (n (%))	7 (14)
Fatigue (n (%))	18 (36)
Drooling (n (%))	35 (70)
Kyphoscoliosis (n (%))	8 (16)

MMSE Mini Mental State Examination, *BDI* Beck Depression Inventory, *UPDRS* Unified Parkinson's Disease Rating Scale, *PD* Parkinson's disease

[a] Higher numbers indicate a greater severity of impairment

significant differences between the Lisbon and Barcelona cohorts were found in the frequency of patients on bromocriptine (Lisbon = six vs. Barcelona = one patients; $p = 0.04$) and in the mean daily dose of levodopa (Lisbon = 934 ± 352.5 mg vs. Barcelona = 688 ± 234.4 mg; $p = 0.01$). The mean daily dose of levodopa did not differ significantly between patients with and without motor

Table 6 Symptoms causing an extreme or severe impact on patients' perceived health status in late-stage PD patients

Impact of symptoms on patients' perceived health status		
Symptoms with extreme impact (score 4)	Falls	Urinary dysfunction
	Unsteadiness	Sweats
Symptoms with severe impact (score 3)	Bradykinesia	Apathy
	Freezing	Anxiety
	Speech problems	Depression
	Dysphagia	Dementia
		Constipation
		Dyspnea
		Pain

Table 7 Medication in late-stage PD patients

	PD patients ($n = 50$)
Levodopa (n (%))	
Total	49 (98)
Monotherapy	18 (36)
In combination	31 (62)
Daily dose of levodopa (mg) (mean (SD))	785 (318)
Range of daily dose of levodopa (mg)	250–1900
Agonists (n (%))	25 (50)
Amantadine (n (%))	9 (18)
Entacapone (n (%))	6 (12)
Selegiline (n (%))	5 (10)
Anticholinergics (n (%))	1 (2)
Brain surgery for PD (n (%))	4 (8)
Neuroleptics (n (%))	25 (50)
Benzodiazepines (n (%))	22 (44)
Antidepressants (n (%))	14 (28)
Rivastigmine (n (%))	2 (4)
Non-neurological medication (n (%))	32 (64)

PD Parkinson's disease

complications. Twenty-five patients (50%) were taking atypical neuroleptics because of delusions and visual hallucinations. Fifteen of them were demented. Clozapine was the most frequently prescribed neuroleptic ($n = 19$), at a mean daily dose of 56.5 ± 71.0 mg/day, while quetiapine was prescribed in five patients (mean daily dose 125 ± 90.1 mg/day). Fourteen patients (28%) were on antidepressants, while nearly half were on benzodiazepines: 56% because of anxiety and 50% because of nocturnal sleep disturbances.

Discussion

As expected, we have found that this cohort of LS-PD had long-standing disease, with severe motor and frequent and severe non-motor symptoms. Levodopa-induced motor

complications were frequent but generally not disabling. Symptoms causing the highest disability, such as falls, postural instability and many non-motor symptoms, were non-levodopa responsive. Medication was mainly targeted at improving motor symptoms, and, in two-thirds of patients, consisted of levodopa associated with other anti-parkinsonian drugs. Dosage of these drugs was probably influenced by the frequent occurrence of neuropsychiatric symptoms, such as psychosis. Although patients reported some benefit from levodopa, this was of limited clinical relevance. The scores in UPDRS-ADL and S&E during *on* and *off*, although statistically significant, showed that patients were highly disabled and dependent on caregivers in either levodopa state. Other treatments were directed to the correction of psychosis, anxiety, sleep disturbances and depression.

Our data do give some insight about the clinical characteristics of LS-PD and may have implications on how we manage this illness. Information on clinical features of LS-PD is relatively sparse [1, 2, 4, 5, 8, 16]. Papapetropoulos and Mash [16] have reported on the frequency of motor complications in a cohort of 61 patients with LS-PD, although only two-thirds of their patients were H&Y greater than three. Recently, the Sydney Multicenter Study [5] reported on the 30 patients surviving after 20 years of follow-up, most in H&Y stage 4. These patients were initially recruited into a clinical trial, which may have influenced entrance characteristics and subsequent management.

The cohort

We selected patients based on motor PD severity, and not disease duration. The mean disease duration (18 years) was longer than previously reported in other studies that included severely disabled patients [4, 17, 18]. However, age at disease onset was similar [1, 4, 18], excluding early disease onset as the cause of prolonged survival. We included more females than males. This excess of women might be related to shorter life expectancy of men compared to women.

Patients' perceived health status and ADL

The symptoms most contributing to diminished perceived health status, in line with other reports [4, 5], were mostly non-levodopa responsive, and for the majority we lack efficacious therapeutic interventions. And even for the ones where treatment is available, such as depression and anxiety, about half were not prescribed any treatment, suggesting that clinicians may have under-recognized or underestimated these symptoms.

Motor symptoms

Most patients had symmetric disease, possibly a sign of PD progression [10]. Bradykinesia had a profound impact on patients' disability, while rigidity was generally mild and rest tremor was uncommon. Falls and related fractures (20%) were common but perhaps lower than expected, probably since the majority of patients (78%) were wheelchair-bound. Our findings are in line with those of a recent meta-analysis, that found a 3-month fall rate of 46% and that falls decreased in later stages of disease [19]. Dysarthria had a great impact on patients' condition, interfering with communication with caregivers, whereas dysphagia was a frequent cause of choking and tube feeding. Pneumonia, frequently caused by aspiration, was the most common cause of death in the Sydney cohort [4, 5], suggesting that an aggressive intervention on dysphagia might prolong survival [20].

Levodopa-induced motor complications

Overall, levodopa-induced motor complications occurred frequently in our cohort (78%), findings similar to those from Papapetropoulos and Mash (88.5%) [16] and from the Sydney studies (95%) [4, 5]. In our cohort, *offs* were characterized by high disability and dependency on caregivers, although they were of short duration. Even so, patients did not value the relative impact of *offs* compared to *ons*, probably because they also were doing poorly in the *on* stage. Dyskinesias were frequent, but troublesome in only a minority, and patients were free of dyskinesias for most of the day. Likewise, in the study of Papapetropoulos and Mash [16], dyskinesias (60.6%) were severe in only six cases. The Sydney studies [4, 5] also reported not disabling levodopa-induced motor complications. They occurred in most at either 15 and 20 years [4, 5], but severe dyskinesias only afflicted 10% of patients, and in just 17% an *off* >75% of the day was reported.

LS-PD cohorts with a high frequency of motor fluctuations, such as ours, may represent a subset of LS-PD with long survival. When comparing moderate-severe motor fluctuators with non-fluctuators, Kempster et al. [21] found that the development of disease milestones (falls, hallucinations, cognitive disability and institutionalization) was determined solely by age, not disease duration or presence of fluctuations. Fluctuators had a significantly longer disease duration when they reached milestones [21]. Our cohort reinforces that patients with fluctuations reach milestones as do patients without fluctuations.

Non-motor complications of PD

Non-motor symptoms, mostly neuropsychiatric and dysautonomic, were prominent in our cohort. The number

of patients with neuropsychiatric symptoms was higher than the one reported by Aarsland et al. (61%) [22], where only a 23% of patients were in a Hoehn and Yahr stage of 4, suggesting that more advanced disease is associated with a higher frequency of neuropsychiatric symptoms. However, the type and relative frequency of symptoms were similar, indicating that the presence of most symptoms is independent of staging [22, 23].

Our figure (62%) for depression is similar to that found in the Sydney studies [4, 5], but higher than the 43% reported by Papapetropoulos et al. [2], in a retrospective study. Possibly, the prominent dysarthria, cognitive impairment, severe hypomimia and apathy might have biased this figure [24].

Almost half (44%) had visual hallucinations at the time of study assessment, consistent with the late stage of their illness [2–5, 23, 25, 26]. The presence of hallucinations probably explains the low doses of agonists, and frequent use of levodopa as monotherapy. Hallucinations were a major cause of morbidity, as 55% of those with hallucinations rated them as causing an extreme or severe impact on their perceived health status. This severe disability is also indirectly expressed in the widespread use of neuroleptics (50%).

Only 50% of the patients were diagnosed with dementia, a percentage lower than in other series that claim inevitability [5]. Diagnosis of dementia was based on clinical examination and not on neuropsychological assessment, and this might explain the differences reported. Our frequency is similar to that found in the Sydney study [4] at 15 years (48%), by Papapetropoulos et al. (50.7%) [2], and by Kempster et al. (55.6%) [21]. It differs from that of the Sydney cohort at 20 years (83%) [5], but in this study the duration of PD was longer, even though the mean age of patients was similar to ours. Besides that, in the Sydney cohort 26 patients were already demented at baseline neuropsychological assessment [5]. It also differs from the one found by Aarsland et al. [27] after 8 years of follow-up (78%). However, these authors [27] calculated the period prevalence and not point prevalence, combining prevalence, incidence and mortality rates. Importantly, the data from Hely et al. [5] and Aarsland et al. [27] are longitudinal which increments its reliability compared to our cross-sectional data collection.

Lack of tremor and absence of depression independently predicted the presence of dementia. Published data has shown better prognosis and preserved cognition in tremor-predominant PD [28, 29]. Depression has been found to correlate variably with cognitive decline [4, 30–32]. We may assume that demented patients are less likely to report or show depression, and that could be an explanation to our findings. As some studies suggest that depression associates with cognitive decline, longitudinal data are essential to disclose how depression and dementia relate to each other at different stages of cognitive function.

Forty-eight patients (96%) had symptoms suggestive of autonomic dysfunction. In a quarter of patients, orthostatism was symptomatic, but syncope was rare, and none was under specific treatment. Prominent urinary dysfunction and constipation, as well as sweats, were very common, and responsible for severe disability. Night sleep problems were not significantly troublesome, contrary to common belief. Pain was uncommon but very disabling, unlike results of two cross-sectional studies that reported higher pain frequencies (62–70%), even though in patients less advanced than ours [33, 34].

Medication

Nearly all patients took levodopa either as monotherapy or in association with other antiparkinsonian drugs, mainly dopamine agonists at low doses. The mean dose of levodopa was in the same range of that in the Sydney cohort [4, 5] and in the study by Papapetropoulos and Mash [16], but much lower than the mean dose of advanced PD patients that are candidates to deep brain stimulation (about 1,100 mg) [35, 36]. Overall, patients still reported some benefit from levodopa intake, namely in motor slowness and tremor. Patients with motor fluctuations had "poor" *ons*, however, with a change in disability between *on* and *off* that was of little clinical relevance. Similar to that reported by others [16], a small portion of our patients had a remission of motor fluctuations. Although we cannot rule out that changes in doses or pattern of the dopaminergics treatment can be responsible for such remission, this finding could be also explained by increasing extranigral pathology along with the disease progression [37, 38].

Shortcomings

We studied a convenience sample of hospital-based patients, who were under the care of our tertiary clinics. Our recruitment rate was low (25 patients per year per center), which strongly suggests that patients withdraw from specialized medical care once they reach an advanced stage. Our results, then, may not be representative for the entire population of LS-PD, namely, we cannot draw any firm conclusion regarding the prevalence of dementia in these late stages of the disease. Additionally, recruiting patients from two countries could have led to a heterogeneous sample. Nonetheless, except in the use of antiparkinsonian drugs, which most likely reflects different prescription practices, the sample was rather homogeneous.

Conclusions

In this hospital-based cohort of LS-PD patients, both motor and non-motor non-levodopa responsive problems were the main cause of disability. Half of the patients were considered non-demented, questioning the inevitability of dementia at late-stage. Levodopa-induced motor complications were frequent though not generally disabling, possibly since swings between *on* and *off* were of small magnitude. Future interventions, either pharmacological or non-pharmacological, research and allocation of funds must focus on non-levodopa responsive aspects of the disease.

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Conflict of interest statement None.

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Dementia and severity of parkinsonism determines the handicap of patients in late-stage Parkinson's disease: the Barcelona–Lisbon cohort

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Keywords:
advanced, caregiver, dementia, disability, handicap, late stage, Parkinson's disease, quality of life

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Background and purpose: Handicap has not been explored as a patient-centred outcome measure in Parkinson's disease (PD). The clinical features and medication use in late stages of PD (LS-PD) were reported previously.

Methods: Handicap, medical conditions, use of healthcare resources and the impact of LS-PD upon caregivers were characterized in a cross-sectional study of LS-PD stages 4 or 5 of Hoehn and Yahr (H&Y). Handicap was measured using the London Handicap Scale (LHS: 0, maximal handicap; 1, no handicap).

Results: The mean LHS score in 50 patients was 0.33 (SD ±0.15). The presence of dementia, the Unified Parkinson's Disease Rating Scale part I score and the H&Y stage in 'off' independently predicted the LHS score (adjusted $R^2 = 0.62$; $P = 0.000$). Comorbidities and past medical conditions were frequent. Thirty-five patients lived at their house. Forty-five received unpaid care. Mean visits to the family doctor in the preceding 6 months were 2.2 (SD ±3.0) and to a neurologist 1.7 (SD ±1.0). Use of other health resources was low. Unpaid caregivers spent much time with patients and reported a high burden.

Conclusion: Handicap could be measured in LS-PD and the LHS was easily completed by patients and caregivers. The high handicap in our cohort was mostly driven by the presence of dementia, behavioural complaints and the severity of non-dopaminergic motor features. Patients visited doctors infrequently and made low use of health resources, whilst unpaid caregivers reported a high burden.

Introduction

There are few published studies on late-stage Parkinson's disease (LS-PD) [1-4]. A hospital-based population of LS-PD has recently been reported by us [3]. These subjects were severely disabled mostly from non-levodopa responsive problems and suffered frequent motor fluctuations and dyskinesias.

The impact that PD has on patients has been addressed using several outcome measures, such as disability, interference in activities of daily living or quality of life (QoL) [5,6]. Handicap, an outcome measure widely used in chronic neurological or non-neurological diseases [7,8], has never been used in PD. The WHO defines handicap as '... a disadvantage for a given individual, resulting from an impairment or a disability, that limits or prevents the fulfilment of a role that is normal, depending on age, sex, and social and cultural factors, for that individual' [9], and thus it is central to the management of patients with chronic diseases [10]. Handicap seems a more understandable concept to patients than QoL and a more meaningful measure of the impact of disease in the health status (HS) of an individual patient. The London Handicap Scale (LHS) is one of the most frequently used instruments to measure handicap [8,11,12] but has never previously been used in PD. It has proven good validity, reliability, sensitivity to change and transcultural validation [11–14].

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The results concerning handicap caused by very advanced PD are reported. In addition, the presence of comorbidities and past medical conditions, health resources use and the impact of disease on caregivers are described.

Patients and methods

Objectives

The primary objective was to quantify the handicap of a hospital-based population of LS-PD patients and to identify its determinants. Secondary objectives were to determine comorbidities and past medical conditions, quantify the use of health resources and assess the impact of disease upon the caregivers.

Study participants

The study participants were Parkinson's disease patients attending the movement disorders outpatient clinics of two university hospitals, one in Barcelona, Spain (Hospital Clínic Universitari), and the other in Lisbon, Portugal (Hospital Santa Maria). PD was diagnosed according to the UK Parkinson's Disease Society Brain Bank Criteria [15]. Patients in stage 4 or 5 of Hoehn and Yahr (H&Y) in 'on' were included (stage 4, patients with severe disability but still able to walk or stand unassisted; stage 5, wheelchair bound or bedridden unless aided) [16]. Patients' informal caregivers (unpaid caregivers) were interviewed. The study was approved by the local ethics committees and written informed consent was obtained.

Study design

This was a cross-sectional study in subjects consecutively recruited during a 24-month period.

Participants' evaluation

Patients

Data on demographics, clinical manifestations and disease management, comorbidities and past medical conditions, and usage of healthcare resources were obtained using a structured questionnaire (interviewing the patients and caregivers), a physical examination form and review of medical charts when needed. Details of other assessments performed in this same group of patients have been reported previously [3]. Briefly, patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Schwab and England (S&E) scale [17], and a structured questionnaire adapted from Witjas *et al.* [18] to assess non-motor symptoms in three domains: behavioural and cognition; dysautonomia; and other (sleep, fatigue, pain, paresthesias, anorexia and drooling). Dementia and depression were diagnosed according to the DSM-IV definitions [19] and rated using the Mini-Mental State Examination [20] and the Beck Depression Inventory [21], respectively.

Handicap was assessed using the LHS [11,12]. This scale was developed to determine the effect of chronic disease on a person's functional ability [8,11–14]. It takes around 10 min to be completed and consists of a self-completed questionnaire, although the descriptions of questions are objective enough for completion by a proxy. The questionnaire has six questions, one for each domain of handicap (mobility, physical independence, occupation, social integration, orientation and economic self-sufficiency), and each question contains six sentences hierarchically describing the degree of handicap; for each question, the patient must choose the most suitable sentence. Each sentence is assigned a scale weight. The questionnaire comprises a matrix of scale weights which when combined give a total score for handicap, to which a constant value of 0.456 is added; the final score ranges from 0 (maximal handicap) to 1 (no handicap).

Caregivers

Informal caregivers were asked to rate the impact of PD on their life (0, no impact; 4, maximal impact) [18] and the time per week they spent caregiving. The time allocated to caregiving was calculated by multiplying number of hours per day by the number of days per week.

Statistical analysis

The software program SPSS 14.0 (SPSS, Chicago, IL, USA) was used. A descriptive analysis was performed of demographic data, of motor symptoms according to UPDRS and a structured questionnaire and non-motor symptoms according to a structured questionnaire adapted from Witjas *et al.,* of the impact of symptoms on perceived HS (impact on perceived HS rated by patients: 0, no impact; 4, extreme impact) [3], of medication use, of associated medical conditions, of patients' residency ('own home', 'relatives home' or 'nursing home') and use of health resources, and of caregiver burden according to time allocated to caregiving and the impact of PD on caregivers' life. A descriptive analysis of the LHS total score and subscores was performed.

A comparison of cohorts from Lisbon and Barcelona was done. The independent samples t test and Mann–Whitney U test were used for comparison of

continuous variables, and the Pearson chi-squared test and Fisher's exact test for differences in proportions. Univariable analysis was performed, and variables associated with the LHS score at a significance level of $P \leq 0.1$ were entered in a multiple linear regression analysis using the LHS total score as dependent variable. Two-tailed P values <0.05 were considered significant.

Results

Patients

Fifty patients were studied. Results on demographics, clinical manifestations and medication use have been reported previously [3] and are shown in Tables 1 and 2.

Handicap

London Handicap Scale values followed a Gaussian distribution with a mean LHS total score of 0.338

Table 1 Demographics and medication use in late-stage PD patients

Characteristic	PD patients (n = 50)
Female, n (%)	27 (54)
Patients from Barcelona, n (%)	28 (56)
Patients from Lisbon, n (%)	22 (44)
Age (years), mean (SD)	74.1 (7.0)
Duration of disease (years), mean (SD)	17.94 (6.3)
Hoehn & Yahr stage[a], n (%)	
4	30 (60)
5	20 (40)
Levodopa, n (%)	49 (98)
Monotherapy	18 (36)
In combination	31 (62)
Daily dose of levodopa (mg), mean (SD)	785 (318)
Range of daily dose of levodopa (mg)	250–1900
Agonists, n (%)	25 (50)
Amantadine, n (%)	9 (18)
Entacapone, n (%)	6 (12)
Selegiline, n (%)	5 (10)
Anticholinergics, n (%)	1 (2)
Brain surgery for PD, n (%)	4 (8)
Neuroleptics, n (%)	25 (50)
Clozapine, n (%); daily dose (mg), mean (SD)	19 (38); 56.5 (71.0)
Quetiapine, n (%); daily dose (mg), mean (SD)	5 (10); 125 (90.1)
Other, n (%)	1 (2)
Benzodiazepines, n (%)	22 (44)
Antidepressants, n (%)	14 (28)
Rivastigmine, n (%)	2 (4)
Non-neurological medication, n (%)	32 (64)

PD, Parkinson's disease.
[a]Scored during 'on' period.

Table 2 Clinical manifestations in late-stage PD patients

Clinical manifestation	PD patients (n = 50)
UPDRS motor 'on', mean (SD)[a, b]	49.18 (13.0)
UPDRS ADL, mean (SD)[b]	
'On'	28.2 (6.3)
'Off'	29.6 (5.8)
S&E, mean (SD)[c]	
'On'	31.0 (15.7)
'Off'	23.2 (14.2)
Asymmetric disease, n (%)	16 (32)
UPDRS limb bradykinesia items, median[b]	3
Limb rigidity, n (%)	32 (64)
Rest tremor, n (%)	8 (16)
Postural tremor, n (%)	25 (50)
Postural instability, n (%)	50 (100)
Freezing, n (%)	31 (62)
Falls, n (%)	25 (50)
UPDRS speech, median[b]	3
UPDRS swallowing, median[b]	2
L-dopa-induced motor complications, n (%)	39 (78)
Wearing-off, n (%)	39 (78)
'Off' duration >75% of the day, n (%)	7 (14)
Dyskinesia, n (%)	31 (62)
Troublesome dyskinesias, n (%)	13 (26)
L-dopa-induced non-motor fluctuations, n (%)	33 (66)
Cognition, mood and behaviour, n (%)	50 (100)
Visual hallucinations, n (%)	22 (44)
Delusion, n (%)	16 (32)
Dementia (DSM-IV), n (%)	25 (50)
MMSE, mean (SD)	17.7 (8.1)
Anxiety, n (%)	25 (50)
Irritability, n (%)	20 (40)
Aggressive behaviour, n (%)	8 (16)
Depression (DSM-IV), n (%)	31 (62)
BDI, mean (SD)	16.8 (5.29)
Symptoms suggestive of apathy, n (%)	28 (56)
UPDRS part I, mean (SD)[b]	6.4 (3.9)
Dysautonomic complications, n (%)	48 (96)
Orthostatic hypotension[d], n (%)	3 (6)
Orthostatism[c] (item 42 of UPDRS), n (%)	13 (26)
Syncope, n (%)	4 (8)
Constipation, n (%)	41 (82)
Urinary dysfunction (incontinence, urgency or retention), n (%)	32 (64)
Hyperhidrosis, n (%)	18 (36)
Sweats, n (%)	18 (36)
Dyspnoea, n (%)	7 (14)
Night sleep problems, n (%)	30 (60)
Diurnal somnolence, n (%)	18 (36)
Pain, n (%)	12 (24)
Drooling, n (%)	35 (70)

PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living; S&E, Schwab and England scale; MMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory.
[a]Scored during 'on' period; [b]higher numbers indicate a greater severity of impairment; [c]higher numbers indicate more independence in the activities of daily living; [d]it was possible to measure arterial blood pressure in 18 patients; [c]item 42 of UPDRS was completed by all patients.

Table 3 Total and sub-scores in the six domains of the London Handicap Scale in late-stage PD patients

	Total	Mobility	Physical independence	Occupation	Social integration	Orientation	Economic self-sufficiency
Mean (SD)	0.338 (0.155)	−0.042 (0.044)	−0.057 (0.003)	−0.047 (0.051)	0.007 (0.031)	0.004 (0.074)	0.013 (0.062)
Median	0.325	−0.036	−0.057	−0.035	0.007	−0.008	0.033
Minimum/maximum	0.044/0.628	−0.108/0.038	−0.061/−0.053	−0.350/0.099	−0.041/0.063	−0.075/0.109	−0.111/0.100
Minimum/maximum possible values for total score[a] and each domain sub-score[b]	0/1	−0.108/0.071	−0.061/0.102	−0.060/0.099	−0.041/0.063	−0.075/0.109	−0.111/0.100

PD, Parkinson's disease.
[a]In the London Handicap Scale total score, 0 indicates total disability and 1 indicates normal function; [b]in the London Handicap Scale sub-scores of the six domains, the minimum value indicates most severe disadvantage and the maximum value indicates no disadvantage.

(SD ±0.155) (Table 3). The most affected domain was orientation.

In simple linear regression analysis, the following variables were significantly correlated with the total LHS score: dementia (DSM-IV) ($P < 0.001$); depression (DSM-IV) ($P < 0.05$); unsteadiness causing severe or extreme impact on patients' perceived HS ($P < 0.05$); falls causing severe or extreme impact on patients' perceived HS ($P < 0.05$); hallucinations ($P < 0.05$); H&Y in 'on' ($P < 0.01$); H&Y in 'off' ($P < 0.005$); patients' residency ($P < 0.05$); UPDRS part I score ($P < 0.01$); UPDRS part II score in 'on' ($P < 0.01$) and 'off' ($P < 0.05$); S&E score in 'on' ($P < 0.001$) and 'off' ($P < 0.01$); and wearing-off ($P < 0.05$). Dementia (DSM-IV) was not correlated with UPDRS part I.

In multiple linear regression analysis using the backwards method, the independent variables that still remained significant were dementia (DSM-IV), UPDRS part I score, H&Y stage in 'off', S&E score in 'on', wearing-off, and falls. The variables that best predicted the total score of LHS in the final model were presence of dementia (DSM-IV) ($r = -0.66$; $P < 0.000$), UPDRS part I score ($r = -0.57$; $P < 0.000$) and H&Y stage in 'off' ($r = -0.47$; $P = 0.001$) (Table 4). This model explained 62% of the variance in the total score of LHS ($P = 0.000$). The Durbin–Watson test and collinearity statistics showed lack of correlation and multicollinearity between the independent variables.

Comorbidities and past medical conditions

Thirty-seven patients (74%) had comorbidities whilst 27 (54%) reported past medical conditions (Table 5). No significant differences in the mean total score of LHS were found between patients with and without past or concomitant medical diseases or those with more than two past or concomitant medical diseases.

Use of health resources

Most patients lived in their home and the majority had an informal caregiver. Patients seldom visited doctors, as the number of visits included those to get prescriptions only, and the use of other health resources was low (Table 6).

Caregivers

Mean time per week spent in informal caregiving was 5 days (SD ±2.57), this meaning 5 days × 24 h/week. Informal caregivers rated the impact of PD in their life as high (mean score 3.5; SD ±0.8), which was significantly correlated with the LHS total score ($r = -0.5$; $P < 0.01$). The domains of LHS that

Table 4 Multiple linear regression model for London Handicap Scale

Independent variables	Unstandardized beta	Standardized beta	SE	95% CI	*P*	Dependent variable	*R*	R^2	Adjusted R^2	*P*
Presence of dementia (DSM-IV)	−0.125	−0.408	0.037	−0.200; −0.051	0.02	Total score in London Handicap Scale	0.8	0.65	0.62	0.000
Score in UPDRS part I	−0.015	−0.368	0.005	−0.024; −0.005	0.03					
Hoehn & Yahr staging in 'off'	−0.115	−0.361	0.034	−0.183; −0.046	0.02					

CI, confidence interval; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 5 Comorbidities and past medical conditions in late-stage PD patients

	PD patients (n = 50)
Comorbidities, n (%)	37 (74)
Patients with ≥2 comorbidities, n (%)	26 (52)
Musculoskeletal diseases, n (%)	20 (40)
Cardiovascular disease, n (%)	14 (28)
Benign prostate hypertrophy, n (%)	8 (16)
Eye cataract, n (%)	7 (14)
Weight loss, n (%)	7 (14)
Skin infection or ulceration, n (%)	5 (10)
Gastrostomy, n (%)	5 (10)
Non-skin cancer, n (%)	3 (6)
Skin neoplasm, n (%)	3 (6)
Miscellaneous, n (%)	7 (14)
Past diseases, n (%)	27 (54)
Patients with ≥2 past diseases, n (%)	10 (20)
Bone fractures in the previous 5 years, n (%)	10 (20)
Pneumonia in the previous 5 years, n (%)	10 (20)
Lower urinary tract infection in the previous year, n (%)	10 (20)
Kidney or bladder disease (urinary infection apart), n (%)	3 (6)
Stroke (ischaemic or haemorrhagic), n (%)	2 (4)
Skin neoplasm, n (%)	1 (2)
Pulmonary embolism, n (%)	1 (2)
Lung disease (pneumonia and embolism apart), n (%)	1 (2)
Miscellaneous, n (%)	6 (12)

PD, Parkinson's disease.

Table 6 Use of health resources in late-stage PD patients

	PD patients (n = 50)
Patients living in their home, n (%)	35 (70)
Patients living in their relatives' home, n (%)	7 (14)
Patients living in a nursing home, n (%)	8 (16)
Patients with an informal caregiver, n (%)	45 (90)
Patients with a paid caregiver, n (%)	19 (38)
Patients with both informal and paid caregiver, n (%)	14 (28)
Patients visited at State-owned hospitals, n (%)	43 (86)
Patients visited at private clinics, n (%)	3 (6)
Patients visited at State-owned hospitals and private clinics	4 (8)
Visits to family physician in the preceding 6 months (includes visits to get prescription only), mean (SD)	2.2 (3.0)
Visits to neurologist in the preceding 6 months (includes visits to get prescription only), mean (SD)	1.7 (1.0)
Hospital admissions in the preceding 12 months, mean (SD)	0.78 (1.0)
Patients using a physiotherapist, n (%)	10 (20)
Patients using a speech therapist, n (%)	3 (6)
Patients using a homecare nurse, n (%)	3 (6)

PD, Parkinson's disease.

resulted in a statistically significant association with caregiver burden were mobility ($r = -0.30$) and orientation ($r = -0.4$) ($P < 0.05$).

Discussion

Handicap was assessed in a cohort of LS-PD patients and it was found that the LHS was useful and easy to apply in these patients. This cohort of LS-PD patients was highly handicapped. Handicap was strongly associated with the presence of dementia (DSM-IV), the severity of mental problems and the severity of parkinsonism in 'off'. These independent variables explained more than half of the variance in the LHS total score. Furthermore, the patients were highly dependent on caregivers who spent much time in care, which resulted in a high burden for caregivers. Overall, health resources were used infrequently.

Handicap

Data about the health burden of PD obtained from the patients' perspective are essential to understand the impact of disease on patients, to complement the data obtained through observer-based instruments and also to assess the effectiveness of therapeutic interventions. The most commonly used subjective outcome measures in PD research have been the perceived HS, generic QoL scales and health-related QoL [22]. The concept of handicap was explored for several reasons [7,11]: handicap is the central aim of rehabilitation [10], which is crucial in progressive and chronic diseases such as PD; although intimately related to the concept of (health-related) QoL, its definition is more objective although keeping the subjective perspective and social interaction context that (health-related) QoL does; it is a focused and concrete concept, easily understandable to patients and caregivers; it is a relevant outcome despite being mostly limited to the context of health experience. In addition, there is good transcultural agreement on the construct of handicap [23] and the objectivity of the concept allows caregivers to fill in the questionnaires in those cases where patients are incapable of doing so. In our study, LHS was easily completed by patients and caregivers. The scores had a normal distribution and no obvious ceiling or floor effects. Dementia (DSM-IV), the severity of mental problems assessed by UPDRS part I [24,25] and the severity of parkinsonism in 'off' according to the H&Y explained a major percentage of the variance in the total LHS score. The H&Y staging is deeply anchored on postural instability, but it also reflects the severity of bilateral parkinsonism [26]. Indeed, others have also found that postural instability is amongst the most disabling problems in advanced PD [1,2,27–29]. Severe disability was previously reported in these same patients using observer-based outcome measures [3] and perceived HS was

also assessed. Results showed that falls and dysautonomia were the symptoms most contributing to poor perceived HS, closely followed by bradykinesia, freezing, bulbar symptoms, dementia (DSM-IV), apathy, anxiety and depression (DSM-IV) [3]. Interestingly, the symptoms most associated with handicap did not fully overlap those most impacting on HS, suggesting that handicap and HS are different constructs for patients' perception of health states. During the revision process that led to the new WHO International Classification of Functioning, Disability and Health (ICF) [30], the term *handicap* was replaced with *participation restriction*, in order to move the emphasis from consequence of disease to functioning, health and limitation of functioning. Nevertheless, the major concept that one's environment influences the functioning of an individual was still embodied in the ICF. In fact, qualitative studies showed a strong transcultural agreement on six domains of participation, and these corresponded to the handicap dimensions [31]; additionally a study by Perenboom and Chorus [32] found that two handicap scales from a pool of 11 existing generic instruments were the ones closest to measuring solely participation. Indeed, one of those two scales was the LHS.

Comorbidities and past medical conditions

Parkinson's disease is associated with significant comorbidity [33]. However, this excess comorbidity is largely confined to conditions associated with PD such as urinary complaints or to complications of PD such as bone fractures [33]. Similarly, the most frequent medical conditions of our patients were related to or complications of PD. In contrast to other studies [33,34], stroke, cardiovascular disorders or diabetes were either low or absent, suggesting that our population may have a long survival due to the lack of potentially fatal medical conditions. 22% of our cohort reported pneumonia in the previous 5 years, a finding in accordance with data showing pneumonia as a major cause of death in PD [2,33,34]. The finding that neither past nor concomitant diseases were associated with a higher handicap strengthens the finding of the impact of PD symptoms on the level of handicap.

Use of health resources

A higher percentage of institutionalized patients was expected in the light of the high UPDRS score, frequent falls, dementia and hallucinations in the cohort, all strong independent predictors of institutionalization [35]. Importantly, low income, the lack of availability of long-stay facilities within the health system and a family-centred organization of Latin societies may combine to explain our findings. Keeping patients at home was accomplished at the expenses of a heavy burden of disease on caregivers and the need for a paid caregiver in many instances.

Our patients consulted doctors fewer times than those in a Dutch study, where PD patients with ≥8 years of disease duration made 1.9 visits to a neurologist and 1.1 to the family physician [36]. Admissions to hospital were few in our sample, taking into account the number of comorbidities and the frequency of psychosis and dementia. Many of these acute medical events might be managed in emergency rooms which could explain the low rate of admissions. A minority made use of other healthcare resources such as speech therapist or homecare nurse, whereas 20% used a physiotherapist which is a low figure in view of the degree of motor involvement [36].

Caregivers

The amount of time spent in caregiving was very high in LS-PD. Accordingly, caregivers' burden and mental health status in PD has been found to correlate significantly with weekly hours of caregiving [37–39]. Two Spanish studies found that caring for patients with disease duration of 7.6–10 years was permanent in 86%–96.5% of the cases [37,39]. Caregiver time is thus a hidden cost in LS-PD, and in other cultures it would mean paid caregiver time. Caring for LS-PD patients had a strong impact on the life of caregivers and this was correlated with the LHS total score, in line with others reporting an increase in caregivers' burden with disease severity [37–40].

Shortcomings

Our low recruitment rate perhaps indicates that there were few LS-PD cases available at the study centres, suggesting that patients withdraw from specialized medical care once they reach later stages of disease. Thus, our results may not be representative for the entire population of LS-PD. Whilst the concept of handicap was addressed, QoL which could have been of interest in order to compare these outcomes of HS was not measured. More information regarding caregivers could have been gathered but our aim was to obtain general data concerning caregivers' burden.

Conclusions

Handicap is an important patient-centred outcome measure which is valuable to use in LS-PD since it provides an overall measure of patients' HS and gives

insight into several domains of disadvantage. The LHS proved to be easily completed and might in the future be explored in earlier stages of disease. Our results show that LS-PD is associated with high handicap and caregivers' burden, and support the notion that cognitive and behavioural symptoms, with a special emphasis on dementia, and severity of parkinsonism, in particular falls and unsteadiness, should be the focus of management in later stages of PD.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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Late-stage Parkinson disease

Miguel Coelho and Joaquim J. Ferreira

Abstract | The cardinal symptoms of Parkinson disease (PD) are asymmetrical bradykinesia, rigidity, resting tremor and postural instability. However, the presence and spectrum of, and disability caused by, nonmotor symptoms (NMS) are being increasingly recognized. NMS include dementia, psychosis, depression and apathy, and are a major source of disability in later stages of PD, in association with axial symptoms that are resistant to levodopa therapy. The model of clinical progression of PD should, therefore, incorporate NMS, instead of being restricted to motor signs and levodopa-induced motor complications. Patients with disabling motor complications are classified as having advanced PD, which has been thought to represent the ultimate stage of disease. However, deep brain stimulation to treat motor complications has dramatically changed this scenario, with implications for the definition of advanced-stage disease. As treatment improves and survival times increase, patients are increasingly progressing to a later phase of disease in which they are highly dependent on caregivers, and disability is dominated by motor symptoms and NMS that are resistant to levodopa. In this article, we review the changing landscape of the later stages of PD, and propose a definition of late-stage PD to designate patients who have progressed beyond the advanced stage.

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Introduction

Parkinson disease (PD) is the second most common age-related neurodegenerative disorder after Alzheimer disease. PD occurs worldwide with an age-adjusted prevalence of 1.8% and similar incidences in females and males.[1] The mean age of onset is about 65 years, with prevalence rising from 0.6% at age 65–69 years to 2.6–3.5% at age 85–89 years.[1,2] Disability in this disease is progressive[3] and associated with increased mortality (relative risk of death 1.6–3.0 compared with matched control populations).[4,5]

The primary pathology of PD is progressive dopaminergic neuronal loss in the substantia nigra, but other neurotransmitter systems (cholinergic, noradrenergic and serotonergic) are also affected.[6,7] Clinically, PD is characterized by the motor symptoms of asymmetrical bradykinesia, rigidity and rest tremor, as well as postural instability later in the disease course.[8] However, nonmotor symptoms (NMS) such as dementia, depression, pain, sleep disorders and dysautonomia increase in frequency and severity in later disease stages.[9] The available pharmacological and surgical treatments substantially improve motor symptoms, but achievement of satisfactory symptomatic control becomes difficult in more-advanced disease stages. Levodopa remains the most potent antiparkinsonian drug, but its long-term use is associated with development of motor complications.[10,11]

This Review discusses data regarding the phenotype of later stages of PD, including the widely accepted advanced-stage PD, which features motor complications, and the less-well characterized subsequent stages, which feature disability 'milestones' in the approximately 5 years preceding death. We focus on the changing landscape of later stages of PD over the past decade, and discuss the emerging concept of late-stage PD. Such aspects of PD are becoming increasingly relevant as neurologists are more often treating patients with very-advanced-stage PD owing to improved treatment and increased survival.

Competing interests
The authors declare no competing interests.

Progression of PD

Traditionally, progression of PD is regarded as an increase in severity of motor symptoms—which can be either levodopa-responsive or levodopa-resistant[12,13]—together with the emergence of levodopa-induced motor complications.[14] This motor progression is nonlinear, with a more rapid decline in motor function in earlier stages compared with later stages.[15,16] A recent study found that an increase of 2.5 points in the motor Unified Parkinson Disease Rating Scale (UPDRS) score,[16] or of 4.3 points in the total UPDRS score, is the minimum change required to be recognized by patients as being clinically significant.[17]

Motor complications

Most patients with PD who receive dopaminergic therapy go on to develop motor complications.[18,19] The frequency of this phenomenon varies among studies, but seems to affect about 40–50% of patients after 4–6 years of levodopa treatment.[18] Occurrence of motor complications is most strongly related to disease duration, and to duration and dose of levodopa treatment.[18,20] However, in the ELLDOPA trial, a substantial number of patients developed motor complications within 9 months of levodopa treatment.[21]

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Key points

- Advanced-stage Parkinson disease (PD) is widely accepted as a term to denote patients with motor complications, but many patients continue to progress to a less well-defined stage
- Late stages of PD are of increasing clinical relevance owing to improved treatment and survival
- Progression of PD is characterized by worsening disability owing to motor complications, nonmotor symptoms (NMS) and motor symptoms that are unresponsive to levodopa
- Disability in late stages of PD is mostly associated with NMS such as dementia, psychosis and dysautonomia, and motor symptoms that are unresponsive to levodopa, such as dysarthria and falls
- We propose a definition of late-stage PD in which patients are highly dependent on caregivers for activities of daily living, owing to motor symptoms or NMS that are resistant to levodopa
- Future research should focus on the pathogenic mechanisms underlying late-stage PD, which could highlight therapeutic targets and potential end points for clinical trials

In advanced stages of PD, motor complications have a considerable impact on quality of life (QoL) and patient disability.[11,22] The domains of QoL that are most affected seem to be mobility, activities of daily living (ADL), stigma and communication.[11] Interestingly, in patients with disease duration of 5–10 years, a higher levodopa dose was associated with better QoL despite an increased prevalence of motor complications.[20] Compared with the general population, PD patients with motor complications had a worse QoL, which deteriorated substantially with disease severity.[23] However, in later disease stages, disability from motor complications seemed to decline relative to disability associated with symptoms that are resistant to levodopa.[24–26] Some studies even found that motor complications remitted in some patients[26,27]—a finding that did not correlate with a reduction in the dose of antiparkinsonian drugs.

Levodopa-resistant symptoms

The clinical progression of PD in later stages is increasingly recognized to be dominated by the emergence or aggravation of symptoms that are nonresponsive to levodopa.[24,25,28–31] These can include NMS such as dementia, psychosis or dysautonomia, and axial motor symptoms such as falls, postural instability or dysphagia. These symptoms are the main determinants of QoL, and are a major source of disability, as well as being risk factors for institutionalization and death.[24–26,32,33] As such, NMS and axial motor symptoms that are resistant to levodopa should be incorporated into the classic model of PD progression.

Sequence of events

Some motor symptoms and NMS tend to progress together, and a study found that a cluster of variables consisting of NMS (cognitive impairment, psychosis, depression, daytime sleepiness, autonomic dysfunction) and axial symptoms was strongly associated with disease progression.[34] These findings suggest that, together, NMS and axial symptoms dominate the clinical picture of late stages of PD, and that they share common pathogenic mechanisms. Intuitively, one thinks that PD starts with prodromal symptoms,[35] followed by unilateral and then bilateral motor symptoms, progressing to motor complications, balance and gait impairments, and finally psychosis and dementia.[25,34] This sequence of events is not, however, a universal rule, although we cannot yet predict with much certainty which patients will, for example, develop dementia before motor complications.

Staging of PD

For several decades, attempts have been made to stage the clinical evolution of PD.[37] In the pre-levodopa era, Hoehn and Yahr developed a staging system to describe clinical function at different stages of disease, including the concepts of disability (functional deficits) and impairment (objective signs).[37,38] The Hoehn and Yahr scale was based on the concept that the severity of parkinsonism depended mainly on the presence of bilateral symptoms and compromise of gait and balance, and that physical independence was ultimately lost owing to postural instability, gait disorder and severe bilateral parkinsonism.[37,38] This scale has been the most widely used tool to stage the severity of parkinsonism,[39] and available data show significant correlations between later Hoehn and Yahr stages and worse scores for QoL and motor impairment.[40,41]

In addition to physical signs, the Hoehn and Yahr scale can capture other important features of PD: when patients reach stage 3, risk of dementia is increased and survival decreases, and total UPDRS scores increase despite drug adjustment.[38,42] Advanced PD is commonly defined as stages 4 and 5 on the Hoehn and Yahr scale, which corresponds with loss of physical independence.[38]

Some weaknesses of the Hoehn and Yahr scale can bias its use. First, incorporation of two indices of severity —impairment and disability—can create ambiguity and difficulty in classifying individual patients, as these indices do not necessarily progress in parallel and may even diverge. Second, the indices are particularly sensitive to postural instability and disorders of lower limbs, thereby increasing the likelihood of overlooking disease progression that is attributable to other motor symptoms or NMS. Last, the Hoehn and Yahr scale broadly categorizes rather than finely grading disease stages, such that an increase in stage does not necessarily entail an overall increase in the patient's motor dysfunction in all cases. As such, patients of different impairment severity can be assigned to the same stage of the Hoehn and Yahr scale, creating clinical heterogeneity in each category.[36]

Overall—and despite its weaknesses—the Hoehn and Yahr scale remains the most robust staging system for PD. Nevertheless, in order to capture the multidimensional causes of disability in later stages of PD, criteria other than the Hoehn and Yahr scale might be needed to define such disease stages, as discussed below.

As an alternative to the Hoehn and Yahr scale, the definition of advanced-stage PD has rested on the presence of motor complications, as their occurrence increases with disease duration and severity, and they are a major source of disability.[11,44,45] In this staging system, patients are usually classified as having advanced-stage disease once motor complications begin,[27] or when these

Table 1 | Baseline features of patients in trials for drug-induced MC and PD-associated dementia

Parameter	Clinical trial of drugs for MC	Clinical trials of deep brain stimulation for MC			Clinical trials for PD-associated dementia			
	Rascol *et al.* (2005)[67]	Deuschl *et al.* (2006)[68]	Weaver *et al.* (2009)[69]	Williams *et al.* (2010)[54]	Aarsland *et al.* (2009)[87]	Leroi *et al.* (2009)[88]	Emre *et al.* (2004)[89]	Emre *et al.* (2010)[58]
Mean age at PD onset (years)	55.0	47.0	50.0	47.6	69.5	65.9	63.0	65.5
Mean age (years)	64.0	60.5	62.3	59.0	76.5	75.7	72.0	72.5
Mean disease duration (years)	9.0	13.5	12.4	11.4	7.0	9.75	9.0	7.0
UPDRS motor score during 'on' time	23.6	18.0	23.0	19.5	11.2*	24.2	34.0	30.0
Mean levodopa treatment duration (years)	7.5	13.5	11.7‡	NA	NA	NA	NA	NA

*Modified motor UPDRS, score range 0–32. ‡Anti-PD drugs, not necessarily levodopa. Abbreviations: MC, motor complications; NA, not available; PD, Parkinson disease; UPDRS, Unified Parkinson Disease Rating Scale.

symptoms become severe enough to substantially impair QoL and independence in ADL.[46] A different definition of advanced-stage PD was recently proposed,[47] which encompasses patients manifesting the cardinal motor symptoms of PD, together with disease-related or drug-induced motor and nonmotor complications. This definition has the advantage of combining disease-related and drug-related symptoms with motor symptoms and NMS in the criteria for advanced PD.

Advanced-stage PD: a moving concept

The advent of deep brain stimulation (DBS) has radically advanced the treatment of motor complications and, therefore, the phenotype and natural history of advanced PD.[48,49]

DBS is a powerful therapeutic intervention for advanced PD, leading to substantial reductions in motor symptoms and motor complications, doses of anti-parkinsonian drugs, and disability.[48–51] DBS also increases QoL of patients with PD[50,52–54] and, more recently, was found to be superior to best medical therapy for the treatment of motor complications.[50,54,55] This motor improvement is sustained overall at 10 years after DBS of the subthalamic nucleus, with the exception of axial signs, which progressively worsen over time.[56]

DBS is neither curative nor neuroprotective, and cannot, therefore, arrest neurodegeneration and clinical progression. In the long term, patients who have received DBS deteriorate owing to axial, cognitive, and behavioural symptoms that are not responsive to treatment.[48,51,56]

Advanced-stage versus late-stage PD

Heterogeneity in advanced-stage PD

The classic concept of advanced-stage PD is broad and, depending on the definition used, encompasses patients with bilateral disease, postural instability and physical dependence (according to Hoehn and Yahr staging) and/or patients with motor complications. Considerable heterogeneity exists among patients with advanced-stage disease, owing to variations in the predominance and severity of motor symptoms and NMS, and in the presence and severity of motor complications, as well as the possible use of DBS.

Disease duration is thought to be a key determinant of the stage of progression, but baseline characteristics of patients with advanced PD who were enrolled in clinical trials for motor complications and PD-associated dementia (Table 1) suggest the involvement of other factors and considerable heterogeneity between patients at this stage of disease.[50,54,55,57,58] These data also highlight the fact that the sequence of events is not universal for all patients and that a subset of patients categorized under the term 'advanced disease' do not fulfil the usual definition of advanced PD. More-nuanced definitions of the late stages of PD are, therefore, needed.

The concept of late-stage PD

Evidence suggests that at least a small subset of patients with advanced-stage PD will progress to a later phase of disease (Figure 1). In this latter stage, disability from motor complications is reduced, because these complications attenuate either naturally or in response to DBS.[25] Disability in the later stage is dominated by levodopa-resistant motor symptoms and NMS,[24,59,60] so that patients no longer fit the classic definition of advanced-stage disease, which is characterized by disabling motor complications. Patients with late-stage PD present with a distinct phenotype, which seems more homogeneous than that denoted by the generic name of advanced-stage disease. They require specialist medical care,[24] although they are usually excluded from clinical trials and even from observational studies.

On the basis of our research in patients who progress beyond advanced PD,[24] we propose the term 'late-stage' to describe patients who are highly dependent on caregivers for ADL, owing to treatment-resistant motor symptoms or NMS. For this definition, we use the Schwab and England ADL Scale,[61] which is a questionnaire that measures patients' perceived functional independence. Scoring ranges from 0% (denoting a bedridden or vegetative

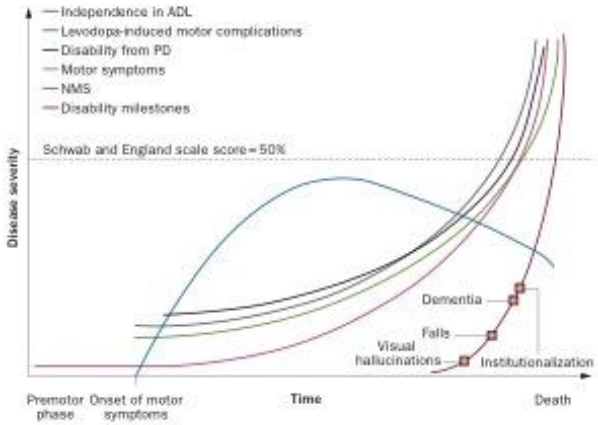

Figure 1 | Progression of PD in the post-levodopa and deep brain stimulation era. A premotor phase of PD is followed by onset of motor symptoms. Over about 5 years, motor symptoms progress in parallel with disability and loss of independence in ADL. During this phase, NMS also progress, but at a slower pace than do motor symptoms. When levodopa-induced motor complications emerge, they become a major source of disability and loss of independence in ADL. The severity of motor complications declines in later stages of PD owing to deep brain stimulation and/or natural resolution. Concomitantly, NMS, bradykinesia and axial motor symptoms that are resistant to levodopa begin to rapidly increase in severity, accompanied by increased disability and loss of independence. Approximately 5 years before death, disability 'milestones', such as visual hallucinations and dementia, emerge in an exponential manner. Abbreviations: ADL, activities of daily living; NMS, nonmotor symptoms; PD, Parkinson disease.

state) to 100% (denoting normal ability with complete independence), with 10% increments. The scale is easy to apply, has moderate to substantial validity and good reliability, and correlates well with UPDRS motor scores.[62,63] Furthermore, the sensitivity of the Schwab and England scale tends to increase with higher Hoehn and Yahr stages, thus requiring smaller sample sizes to compare patients in more-advanced Hoehn and Yahr stages.[62]

Our proposed operational definition of late-stage PD is a score on the Schwab and England Scale of less than 50% during periods of adequate symptom control ('on' period). A score of 50% corresponds with the patient requiring help with half of their chores and experiencing difficulty with all activities. A score of 40% corresponds with the patient being highly dependent on support from carers, able to assist with all chores, but unable to complete most tasks alone.[61]

We are aware that the designation of 'late-stage' to define the ultimate phase of PD deserves further discussion by clinicians, researchers and patients in order for all parties to reach consensus on its appropriateness, understandability and utility. We think that the Schwab and England Scale and a 50% threshold are suitable, but discussion and validation is also required.

Clinical phenotype of late-stage PD

Both cross-sectional and longitudinal data show that disability in more-advanced stages of PD is mainly determined by motor symptoms and NMS that are resistant to levodopa.[24–27,51,57,58,80,64,65] The severity and frequency of NMS seem to increase with advancing disease.[24,50,51,58,80,65,66] The PRIAMO study found that from Hoehn and Yahr stage 1 to stage 4–5, the frequency of NMS increased in 11 NMS domains (gastrointestinal, urinary, pain, sleep, fatigue, apathy, attention and memory, skin symptoms, psychiatric, respiratory, and miscellaneous), but not in the domain of cardiovascular symptoms.[59] For example, 43% of patients at Hoehn and Yahr stage 1 experienced urinary symptoms, compared with 90% of those at stage 4–5. Similarly, 61% of patients at Hoehn and Yahr stage 1 reported psychiatric symptoms, compared with 84% of patients at stage 4–5.[59]

A study on neuropsychiatric symptoms in patients with PD also found that the severity of depression, dementia and psychosis increased with disease severity.[66] Interestingly, this study found that patient age, as well as Hoehn and Yahr stage, influences disease severity. The types and relative frequencies of most neuropsychiatric symptoms, however, seem to be similar across all stages, indicating that the presence (but not the severity) of these symptoms is independent of staging.[26,67,68]

The Sydney cohort study provided 20-year follow-up data on individuals with PD who were initially enrolled in a clinical trial for levodopa-naive patients.[24,25] In a report of outcomes at 15 years,[24] prevalence figures were 81% for falls, 79% for daytime sleepiness, 50% each for hallucinations, depression and choking, 48% for dementia, and 41% for urinary incontinence. Among the 30 patients surviving until 20 years of follow-up,[25] falls, freezing, dementia and moderate dysarthria were each seen in over 80%, hallucinations, excessive daytime sleepiness and urinary incontinence were each experienced by more than 70%, and choking occurred in 48%. Motor complications were frequent at 20 years, affecting 95% of patients, but were not a major cause of disability.[24,25]

In fact, results from several studies suggest that the severity of motor complications decreases as disease progresses, which could explain in part the increased importance of NMS in later stages of PD.[24,26,27,69–71] We have reported comparable findings in our cohort of 50 patients with PD who have a mean disease duration of 18 years.[28] The symptoms with the greatest impact on perceived health status were falls, unsteadiness, urinary dysfunction and excessive sweating.

Disability milestones in late-stage PD

Disability milestones were defined by Kempster *et al.* as symptoms of disease advancement that are likely to require additional medical attention.[69] Motor symptoms and NMS that are nonresponsive to levodopa are the most reliable predictors of nursing home placement and mortality.[24,28,72–74] The strongest independent predictors of institutionalization and death are postural instability and falls, dementia, and hallucinations.[24,28,30,72–74] Moreover, two clinicopathological studies showed that four disability milestones (visual hallucinations, falls, dementia and institutionalization) tend to cluster together in the late phase of PD and precede death by around 5 years (Figure 1, Table 2).[69,75] This time-locked relationship

Table 2 | Parkinson disease disability milestones in selected longitudinal cohorts

Variable	Sydney cohort, 15 years (2005)[24]	Sydney cohort, 20 years (2008)[25]	Kempster et al. (2007, 2010)[68,75]	Stavanger Parkinson Project (Norwegian cohort)*
Number of patients	52	30	129	230 (in the baseline cohort)
Age	71	74	75.5	73.5 at baseline
Duration of follow-up	15.2	20	NA	16 (longest report)
Visual hallucinations				
Age at onset	66.7‡	NA	70.4‡	77.8‡ (for those with hallucinations)
Time to onset	10.7	NA	8.5‡	13.0 (for those with hallucinations)
Falls				
Age at onset	67.5‡	NA	71.4‡	NA
Time to onset	11.5	NA	9.5‡	NA
Residential home admission				
Age at admission	NA	71.6§	72.2‡	NA
Time to admission	NA	9.6§	10.5‡	NA
Dementia				
Age at onset	75.2	71.6	72.2‡	78.4
Time to onset	15.1	10.9	10.5‡	13.8
Death				
Age at death	75.5	76	75.5	81.1
Time to onset	12.2	12.4	13.7	15.8 (median)

Apart from numbers of patients, all data, unless otherwise stated, represent mean values in years. *Figures for this table were extracted from the many reports published by the Stavanger Parkinson Project. §We calculated these values on the basis of the data provided in the original studies. ‡Estimated value for initial sample. Abbreviation: NA, not available.

between occurrence of these four disease milestones and death seems to be independent of age at disease onset, disease duration, and age at death.[69,75] On average, the milestones preceded death by the following time intervals: 5.1 years for visual hallucinations, 4.1 years for falls, 3.3 years for dementia, and 3.3 years in the case of institutionalization.[75] The main difference between patients was the milestone-free duration of disease. Patients with earlier disease onset had a longer disease duration before the occurrence of milestones and death, a stronger response to levodopa, and more-severe motor complications, whereas patients with later disease onset had a shorter disease course, a weaker response to levodopa, and no motor fluctuations.[68] Thus, a late phase of PD seems to progress in the same fashion regardless of the preceding disease course.[68,75]

Late-stage PD in clinical practice

The prevalence of late-stage PD is likely to increase in the future owing to better general health care, increased longevity, and better clinical management of PD.[76] Patients at this stage of disease will be a heavy burden for families and health-care systems, and caregivers will require specialist training. Nevertheless—and perhaps importantly—patients tend to withdraw from specialized medical care once they reach a very advanced stage of PD, for reasons that remain unclear. Practising clinicians will face considerable challenges in managing these patients and their caregivers.

Clinical assessment and therapeutic management of patients with late-stage PD should focus on such problems as falls and postural instability, urinary dysfunction, freezing, bradykinesia, dysarthria and choking, dementia, psychosis, excessive daytime sleepiness, apathy, depression and anxiety. Treatment for motor complications should be less of a priority (Table 3).[24,26–28,31,59,60,65,66] Clinicians should be proactive in asking patients and caregivers about NMS, as these symptoms are often not declared to health-care professionals.[77] Differential diagnosis and rigorous ascertainment of dementia, apathy, depression and even psychosis is particularly difficult in this population, owing to severe dysarthria and daytime somnolence.[24,26,59,60,66] For other symptoms, the situation is more clear-cut: bradykinesia is usually severe whereas rigidity is either absent or mild, which could assist in making a differential diagnosis;[26] notably, reliance on the presence of rigidity could mislead judgments on the severity of parkinsonism.

Effective treatments are lacking for most levodopa-resistant symptoms. Pharmacological management is further complicated by adverse effects—namely, psychosis and excessive daytime sleepiness—induced by antiparkinsonian drugs. Management strategies should aim for regimen simplification, focusing on problematic symptoms for which efficacious treatments are available. For example, in our study of 50 patients with late-stage PD, levodopa was taken as monotherapy in 36% of patients, and 50% were taking neuroleptics, mainly clozapine.[24]

Late-stage PD in clinical research

The phenotype of PD changes considerably in later stages, and the symptoms that contribute most to disability in

Table 3 | Frequency of drug-induced motor complications and nonmotor symptoms in selected studies

Variable	Coelho *et al.* (2010)[26]	Sydney cohort, 15 years (2005)[24]	Sydney cohort, 20 years (2008)[25]	Kempster *et al.* (2010)[75]	Kempster *et al.* (2007)[69]	Papapetropoulos *et al.* (2005)[21]	Stavanger Parkinson Project*	Katzenschlager *et al.* (2008)[89]
Motor fluctuations	39 (78)	50 (96)	30 (100)	NA	62 (64.0)	32 (47.8)	53 (22.1) at 9.1 years of disease duration	56 (53.3)
Dyskinesias	31 (62)	49 (94)	30 (100)	NA	60 (61.8)	28 (41.8)	NA	59 (56.2)
Troublesome or moderate–severe dyskinesias	13 (26)	6 (12)	3 (10)	NA	NA	NA	NA	38 (36.2)
Dementia	25 (50)	25 (48)	25 (83)	70 (54) with cognitive disability	54 (55.6) with cognitive disability	34 (50.7)	21 (46.6) of those evaluated at 12 years	27 (24.7)
Falls	25 (50)	41 (81)	27 (87)	45 (35)	32 (33.0)	39 (58.2)	NA	NA
Visual hallucinations	22 (44)	26 (50)	23 (74)	77 (61)	57 (58.7)	35 (52.2)	12 (48.0) of those evaluated at 12 years	NA
Depression	31 (62)	22 (54% of those tested)	15 (50) on antidepressants	NA	NA	29 (43.3)	19 (24.0) at 17.0 years of disease duration	NA
Urinary dysfunction	32 (64)	22 (41)	22 (71)	NA	NA	19 (28.4) had autonomic dysfunction	n/a	NA
Daytime sleepiness	18 (36)	41 (79)	21 (70)	NA	NA	NA	40 (45.0) at 16.8 years of disease duration	NA
Dysphagia	34 (68)	"Common"	15 (50) had choking	NA	NA	NA	n/a	NA
Mean UPDRS motor score (SD)	49.2 (13)	41.2 (SD NA)	NA	NA	NA	NA	47.1 (20.7) at 16.8 years of disease duration	NA

Apart from UPDRS motor scores, values shown in the table refer to numbers of patients, and values in brackets express the number of patients as a percentage of the total number of patients in the cohort. *Figures for this table were extracted from the many reports published by the Stavanger Parkinson Project. Abbreviations: NA, not available or not applicable; UPDRS, Unified Parkinson Disease Rating Scale.

later stages differ from those in less-advanced and early stages.[24,26–28,31,59,60,63,64] These changes probably reflect the dynamics of neurodegeneration over time, together with the effects of antiparkinsonian drugs.[76,78] In this sense, late-stage PD is a good clinical model to identify the symptoms that cause most disability, and even mortality, in patients who are severely disabled, highlighting the symptoms that should be targeted at an earlier stage of disease. Follow-up of patients in later stages will be valuable in estimation of the rate of motor and nonmotor progression in advanced disease, which is known to differ from that in earlier stages.[45]

Pathogenesis and neuropathology of late-stage levodopa-unresponsive symptoms are key areas for future PD research. Loss of dopaminergic neurons in the substantia nigra pars compacta is considered to be the key biological substrate for the classic motor features of PD.[79] However, extranigral involvement has been extensively documented in PD, and has been implicated in the pathogenesis of levodopa-unresponsive motor symptoms and NMS.[58,75,80–82] For example, loss of cholinergic neurons in the pedunculopontine nucleus and nucleus basalis of Meynert is thought to be crucial in the pathogenesis of the cognitive impairment, attention deficit, postural instability and falls, and visual hallucinations that are observed in late-stage PD.[83,84] These emerging data have already led research to encompass neuronal systems beyond dopaminergic pathways.

The Braak staging system[85] suggests that the progression of α-synuclein accumulation follows a consistent pattern, beginning in the gut and gastric autonomic plexus of Meissner and olfactory nerve endings, ascending rostrally and ultimately reaching cortical areas. However, the presence of Lewy bodies containing α-synuclein in the cortex is neither necessary nor sufficient for impaired cognition,[81,85] which questions the validity of the Braak staging system to explain all symptoms of PD.

The importance of future research on disability milestones is twofold. First, it might promote the identification of new therapeutic targets for drug development. Second, these milestones may represent good candidates for clinical end points of future trials on disease progression.[35] Disease milestones are, however, associated with considerable problems, which merit discussion. Therapeutic interventions aimed at disease milestones may lack efficacy on functional outcomes and disability, owing to the advanced stage of disease at which these events occur. Moreover, if such milestones are used as end points for clinical trials of disease-modifying therapies, the experimental intervention would probably have to

be initiated early in the disease course to allow a reasonable follow-up time in which to measure outcome. Such lengthy trials risk a high drop-out rate, face the threat of a change in clinical management of PD, and are expensive.

Conclusions

Mounting evidence suggests that at least a subset of patients with PD will progress to a late phase of disease in which disability is dominated by levodopa-resistant motor symptoms and NMS (Figure 1). This late-stage PD is characterized by a clinical phenotype that does not fit the common concept of advanced PD. Some patients who enter late-stage PD will have had longer disease duration than other patients at the same disease stage, with earlier disease onset and motor complications that may, at some point, justify DBS because of severe disability. DBS will not, however, prevent the emergence of other sources of disability as disease progresses. Another group of patients will have had a shorter disease course, with older age at onset and few or no motor complications, and this group will eventually enter late-stage PD without prior DBS.

Among the features of late-stage PD, falls, hallucinations, dementia and institutionalization represent milestones that start an exponential curve of disease progression, ending in death within approximately 5 years. Age at onset and disease duration only seem to determine how long the patient will remain milestone-free. Identification of the most disabling symptoms has direct implications for the focus of clinical care and research.

A universal feature among patients with late-stage PD is complete loss of independence. We propose that this stage of PD should designate patients who are very dependent on caregivers for ADL, scoring less than 50% on the Schwab and England Scale during the 'on' period. This definition focuses on functional consequences of motor and nonmotor parkinsonism, in contrast to late stages on the Hoehn and Yahr Scale, which place emphasis on postural instability and gait dysfunction. Discussion and validation of a suitable definition of late-stage disease should be the topic of future work, to address this increasingly common facet of the PD landscape.

Review criteria

We searched PubMed for full-text papers published in English and French between January 1966 and April 2012 using the terms "Parkinson disease" and "advanced", "late stage", "staging", "progression", "nonmotor symptoms", "nondopaminergic", "environmental" and "pathology". Reference lists of identified papers were manually searched for additional relevant studies.

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Review

Expert Opinion

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Treatment options for non-motor symptoms in late-stage Parkinson's disease

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Late-stage Parkinson's disease is characterised by patients dependent on caregivers for their activities of daily living, even under the best levodopa benefit. Non-motor signs that overcome the well-known motor signs of Parkinson's disease dominate late-stage Parkinson's disease and few systematic data exist for the treatment of these signs. The objective of this study was to review the treatment options for Parkinson's disease dementia, psychosis, falls, bone fractures, joint and skeletal deformities, pain, orthostatic hypotension, gastrointestinal abnormalities and urological dysfunction in late-stage Parkinson's disease. The study analysed the available controlled clinical trials for the above medical conditions. When absent, data from case series and the authors' own experience was considered. Few controlled clinical trials specifically addressed late-stage Parkinson's disease as a target population. There is a need for therapeutic data on the symptoms that most afflict late-stage Parkinson's disease patients.

Keywords: bone fractures, dementia, dysautonomia, falls, late-stage Parkinson's disease, pain, psychosis

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1. Introduction

The cardinal signs of Parkinson's disease are asymmetrical bradykinesia, rest tremor, rigidity and postural instability. Non-motor symptoms such as dementia, orthostatic hypotension and urinary dysfunction also occur frequently, mainly in advanced stages of the disease [1,2].

Disability in Parkinson's disease is progressive due to the non-existence of an efficacious intervention to slow disease progression. Levodopa still remains the most effective drug for the symptomatic treatment of motor Parkinson's disease. Yet, the emergence of motor complications and the lack of benefit in non-motor symptoms limits its usefulness and adds further disability [3,4]. Although nearly 95% of patients experience motor complications in the later stages of Parkinson's disease, the non-motor symptoms appear to be the ones most contributing to disability [5].

The first attempt to stage Parkinson's disease according to levels of impairment or disability was done in the seminal paper by Hoehn and Yahr [6] and it still holds today despite its shortcomings [7]. The Hoehn and Yahr staging does not take into account motor complications, since it was defined before the levodopa era [6]. Another classification currently used, but lacking formal definition, considers three stages in Parkinson's disease: early, stable and advanced. Under this system, patients reach the advanced stage when they start fluctuating. Therefore, the advanced stage includes early fluctuators who are moderately disabled and far advanced patients who are much more disabled.

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The extreme of this spectrum, designated by late-stage Parkinson's disease, should be distinguished from the early fluctuators, because those patients have very particular needs concerning healthcare. Late-stage Parkinson's disease refers to patients who are dependent on caregivers for most of their activities of daily living, even under the best levodopa benefit (Hoehn and Yahr stage IV or V in an on period) [6]. At most, these patients will still be able to stand or walk unassisted for a short distance. In addition, non-motor symptoms are usually more frequent and severe than in less advanced stages [2,8].

This definition is based on a high level of disability, which is not contingent to the kind of impairments causing it. Yet, since it is anchored to the Hoehn and Yahr staging [6], it implies the presence of severe motor impairments. Nonetheless, it is known that non-motor impairments are probably the most important determinants of disability in later stages of Parkinson's disease [5].

In future years, an increase in the prevalence of late-stage Parkinson's disease is to be expected [9,10] and this population will represent a heavy burden for their families and the healthcare system. Even so, little attention has been focused on the management of late-stage Parkinson's disease and these patients are not usually captured in clinical trials.

Considering non-motor symptoms as the main cause of disability in far advanced stages [5] and that motor complications have been recently and deeply reviewed elsewhere [11-15], this study intends to review the available treatment options for non-motor symptoms in late-stage Parkinson's disease. The study chose those most potentially contributing to disability in this population: dementia, psychosis, falls, bone fractures, joint and skeletal deformities, pain, orthostatic hypotension, gastrointestinal abnormalities and urological dysfunction.

This review has included only data based on controlled clinical trials. An exception is made in the Expert Opinion section, where data from case series and personal experience were incorporated.

2. Management of late-stage Parkinson's disease

2.1 Dementia

Patients with clinical suspicion of Parkinson's disease dementia should have a blood and urine work-up, a neuroimaging study (brain CT or MRI) and their medications reviewed in order to exclude treatable causes of cognitive decline.

If a work-up is negative, specific pharmacotherapy could then be tried. The best-studied drugs in Parkinson's disease dementia are the acetylcholinesterase inhibitors rivastigmine and donepezil. There are no controlled clinical trials on galantamine or memantine for Parkinson's disease dementia [16].

2.1.1 *Rivastigmine*

A 24-week, randomised, double-blind, parallel-group, placebo-controlled trial [17] was conducted in 541 patients with mild-to-moderately severe dementia with onset at least 2 years after diagnosis of Parkinson's disease. A total of 131 patients discontinued the study prematurely, mainly due to adverse events (17.1% of patients on rivastigmine and 7.8% of patients on placebo). Improvements favoured rivastigmine for the Alzheimer's Disease Assessment Scale (ADAS – cog) ($p < 0.001$) and the Alzheimer's Disease Cooperative Study-Clinician's Global Impression of Change Scale (ADCS – CGIC) ($p = 0.007$). The most frequent adverse events were nausea (29% on rivastigmine and 11.2% on placebo) ($p < 0.001$) and vomiting (16.6% on rivastigmine and 1.7% on placebo) ($p < 0.001$), while serious adverse events were similar between the groups. Rivastigmine was associated with parkinsonism exacerbation (27.3 versus 15.6%) ($p = 0.002$), mainly tremor (10.2 versus 3.9%) ($p = 0.01$), but this was not clinically relevant. An active extension study [18], with assessments at 48 weeks, replicated the above results.

2.1.2 *Donepezil*

A randomised, double-blind, cross-over, placebo-controlled trial included 22 patients who had mild-to-moderate dementia developing ≥ 12 months after parkinsonism [19]. Donepezil had a statistically non-significant improvement for the ADAS-cog ($p = 0.18$). The scores in the Mini Mental State Examination (MMSE) ($p < 0.004$) and the Clinical Global Impression of Change ($p < 0.005$) significantly favoured donepezil compared to placebo, but the same was not true for the Mattis Dementia Rating Scale or the Brief Psychiatric Rating Scale. Adverse events occurred equally in both groups, the most frequent being worsening of psychosis and agitation [19].

A randomised, double-blind, cross-over, placebo-controlled trial [20] enrolled 14 Parkinson's disease patients with clinical evidence of impairment in memory (an MMSE score of 16 – 26) and at least one other cognitive domain, which had an onset ≥ 12 months after parkinsonism. Donepezil resulted in a significant improvement in the scores for the MMSE ($p = 0.01$) and the Clinician's Interview Based Impression of Change plus Caregiver Input (CIBIC$^+$) ($p = 0.03$). Three patients on donepezil withdrew due to adverse events. Parkinsonism did not aggravate with donepezil.

Another randomised, double-blind, parallel, placebo-controlled, 18-week trial [21] enrolled a mixed population of 16 Parkinson's disease patients with either a diagnosis of dementia or cognitive impairment associated with Parkinson's disease, but the authors did not state the interval between parkinsonism and cognitive impairment onset. Four patients on donepezil withdrew due to adverse events (parkinsonism aggravation = 1). Significant differences favouring donepezil were found only in the memory subscale of the Dementia Rating Scale ($p < 0.05$).

2.2 Psychosis

In patients presenting with psychosis, a good history is key in identifying the causes. Attention should first be drawn

to any recent change in medication, to metabolic aetiologies and to infections. Brain CT or MRI may prove necessary to exclude a structural lesion. Those patients with drug-induced psychosis should be started on antipsychotics, when no further reduction of antiparkinsonian medication is possible due to motor symptoms. The choice should be among atypical neuroleptics, as classical antipsychotics severely worsen parkinsonism.

There are six marketed atypical neuroleptics: clozapine, quetiapine, risperidone, olanzapine, ziprasidone and aripiprazole. controlled clinical trials are only available for clozapine, quetiapine and olanzapine [16]. A randomised clinical trial comparing clozapine with olanzapine was prematurely stopped because of a severe deterioration in parkinsonism with olanzapine [22]. Case series reporting on risperidone [23,24], ziprasidone [25-27] and aripiprazole [28-30] have described a deterioration in motor function with these drugs.

2.2.1 *Clozapine*

The Parkinson Study Group [31] randomised 60 patients with Parkinson's disease and drug-induced psychosis in a parallel-group, double-blind, 4-week trial to either placebo or low-dose clozapine. The patients had a mean age of 71 years. The psychosis outcome measures were highly statistically significant in favour of clozapine compared to placebo. Regarding safety, six drop-outs occurred: for clozapine these were due to reversible leucopaenia (one patient), myocardial infarction (one patient) and sedation (one patient), while for placebo these were due to an increase in psychosis (two patients) and pneumonia (one patient). The mean neutrophile white cell blood counts and orthostatic blood pressures were similar in both treatment arms, but there was a significantly small increase in the heart rate with clozapine. Important safety issues further arose during and after the extension phase on clozapine (n = 53) with one drop-out due to reversible leucopaenia and nine deaths due to stroke (one patient), cardiac arrest (one patient), pneumonia (two patients), bronchitis (two patients) and unknown causes (three patients). Clozapine was not associated with parkinsonism aggravation.

A randomised, parallel, placebo-controlled trial [32] consisting of a double-blind phase (4 weeks) followed by an open-label period (12 weeks) enrolled 60 patients with an MMSE score $\geq$ 20 who were experiencing drug-induced psychosis. Primary outcome measures significantly favoured clozapine compared to placebo. Overall, adverse events were more frequent with placebo, though somnolence and reversible neutropenia (two patients) were more frequent with clozapine. Two patients died (one sudden death and one due to aspiration pneumonia). Once again, the Unified Parkinson's Disease Rating Scale (UPDRS) motor scores did not differ between treatments.

Other than leucopaenia, the use of clozapine has been associated with severe myocarditis and cardiomyopathy [33-35], acute interstitial nephritis [36,37] and venous thromboembolism [38].

2.2.2 *Quetiapine*

Thirty-one Parkinson's disease patients with drug-induced psychosis and a MMSE score > 21 were randomised to placebo or quetiapine in a double-blind, parallel-group, placebo-controlled, 12-week study [39]. The results did not show significant differences in the efficacy measures between quetiapine and placebo. Another trial that included 58 patients with drug-induced psychosis (29 patients demented) found similar results [40].

2.3 Falls

Falls in late-stage Parkinson's disease may arise due to gait impairment, namely freezing of gait, postural instability, involuntary movements such as dyskinesias or foot dystonia, orthostatic hypotension or psychosis and confusion [41]. An approach to falls should begin by eliminating precipitant factors such as drug-induced psychosis, taking general measures such as removing domestic hazards or adjusting antiparkinsonian therapy [41]. This study found controlled clinical trials using falls as an outcome for the interventions outlined below.

2.3.1 *Physiotherapy*

Two systematic reviews assessed the efficacy of physiotherapy compared to placebo or no intervention in Parkinson's disease [42,43]. The authors found insufficient evidence to support or refute the use of physiotherapy in Parkinson's disease, while another systematic review [44], using a broader definition for 'exercise therapy', concluded that these interventions are probably effective in improving functional outcomes, though this improvement is small and transitory.

Nieuwboer *et al.* [45] included 153 Parkinson's disease patients in a single-blind, randomised, cross-over trial in order to evaluate the use of a home physiotherapy programme, compared to no intervention on gait and gait-related activity (the RESCUE trial). Patients had mild-to-severe postural instability, no cognitive impairment and no unpredictable and longlasting off periods. The primary outcome was the posture and gait score, a composite score of the gait and balance UPDRS items. Falls were a safety measure. The results did not show a significant change in the number of falls with the use of physiotherapy, compared to no intervention ($p = 0.4$).

Protas *et al.* [46] conducted an 8-week, randomised, parallel, assessment-blinded, no intervention-controlled trial in order to assess the efficacy of gait and step perturbation training in reducing the number of falls and improving gait in 18 men with Parkinson's disease. The trial included patients who had a postural instability gait-predominant Parkinson's disease and experienced freezing episodes or had a history of falls and were cognitively well. The results showed a nonsignificant trend to fewer falls with the active intervention compared to the control group.

2.3.2 Occupational therapy

Two systematic reviews [42,47] found insufficient evidence to support or refute the use of occupational therapy in Parkinson's disease compared to placebo or no intervention. Instead, another systematic review [44] found that 'exercise therapy', including occupational therapy, probably had a small and transitory benefit in improving functional outcomes in Parkinson's disease.

2.3.3 Risedronate

Please refer to the section below on Bone Fractures.

2.3.4 1α-Hydroxyvitamin D_3

Please refer to the section below on Bone Fractures.

2.4 Bone fractures

Bone fractures associated with osteoporosis and resulting from falls contribute to immobilisation, which in turn further aggravates osteoporosis and the risk of future falls [41]. Prevention of bone fractures is a result of avoiding falls (see above) and reducing osteoporosis.

2.4.1 Alendronate

Sato *et al.* [48] conducted a 2-year, randomised, double-blind, parallel, placebo-controlled trial in order to evaluate the efficacy and safety of the combined therapy alendronate plus vitamin D_2 (ergocalciferol) in reducing the risk of hip fractures and controlling osteoporosis. The trial included 288 elderly women with Parkinson's disease and excluded patients in Hoehn and Yahr stage 5 [6]. The patients were randomised to alendronate (5 mg/day) plus ergocalciferol (1000 IU/day) or placebo plus ergocalciferol (1000 IU/day). Withdrawals were similar between the groups. The incidence of hip fractures was four patients in the alendronate arm versus 14 patients in the placebo arm. The patients' bone mass density increased 3.1% in the alendronate group and decreased 2.8% in the placebo group ($p < 0.0001$). The adverse events with alendronate were leucopenia (one patient), oesophagitis (two patients) and diarrhoea (three patients), while three patients on placebo suffered from abdominal pain. No serious adverse events occurred.

2.4.2 Risedronate

Sato *et al.* [49] evaluated the efficacy and safety of risedronate in the risk of hip fractures and osteoporosis in 242 elderly men with Parkinson's disease in a 2-year, randomised, double-blind, parallel, placebo-controlled trial. Patients in Hoehn and Yahr stage 5 [6] were excluded. Patients were randomised to risedronate (2.5 mg/day) plus ergocalciferol (1000 IU/day) or placebo plus ergocalciferol (1000 IU/day). Withdrawals were similar between the groups. The incidence of hip fractures was three patients with risedronate versus nine patients with placebo. There was no significant difference in the number of falls between treatments. The patients' bone mass density increased 2.2% in the risedronate group and decreased 2.9% in the placebo group ($p < 0.0001$). The adverse events with risedronate were abdominal pain (four patients) and oesophagitis (three patients), while three patients on placebo suffered from abdominal pain or discomfort. No serious adverse events occurred.

2.4.3 1α-Hydroxyvitamin D_3

Sato *et al.* [50] tested the efficacy and safety of 1α-hydroxyvitamin D_3 ($1\alpha(OH)D_3$, an active form of vitamin D) in increasing the bone mass density and in reducing the incidence of non-vertebral fractures in a double-blind, randomised, placebo-controlled trial. Patients in Hoehn and Yahr stage 5 [6] were excluded. Eighty-six Parkinson's disease patients were randomised to either $1\alpha(OH)D_3$ (1 μg/day) or placebo. After 18 months the incidence of fractures was significantly less in the active arm compared to placebo (one versus eight, respectively) ($p = 0.003$). The patients' bone mass density decreased 1.2% in the treatment group versus 6.7% in the placebo group ($p < 0.0001$). The number of falls was similar between both treatments. The authors did not report the occurrence of adverse events.

2.5 Joint and skeletal deformities

Several joint and skeletal deformities affect Parkinson's disease patients in later stages of the disease, namely striatal hand and foot, camptocormia (bent spine), Pisa syndrome (or pleurothotonus, a persistent flexion of the body and head to one side and axial rotation of the trunk), scoliosis and anterocollis [51]. These deformities have a differential diagnosis from lesions from rheumatoid arthritis or orthopaedic disorders. The available treatment options include antiparkinsonian drugs, botulinum toxin, baclofen and benzodiazepines, orthopaedic surgery and functional neurosurgery, although none has been tested under a controlled clinical trial protocol. Shoulder lesions, such as frozen shoulder and rotator cuff syndrome, are also experienced by late-stage Parkinson's disease patients and will mainly cause pain and limitation of joint movement (refer to section on Pain) [52,53].

2.6 Pain

The overall approach to pain in Parkinson's disease begins by individualising the type of pain the patient is reporting. Pain in Parkinson's disease can be categorised as either dystonic-associated or non-dystonic-associated pain, such as central, neuropathic or radicular, musculoskeletal and akathisia discomfort [54]. The choice of pharmacological and non-pharmacological interventions will depend on the above categories of pain, taking into consideration the possible coexistence of different pain syndromes in the same patient. As most pain is usually associated with a worsening of motor disability, adjustment of antiparkinsonian medication is generally the first step in controlling Parkinson's disease-associated pain [54,55]. No controlled clinical trials on the treatment of pain in Parkinson's disease were found.

2.7 Orthostatic hypotension

Orthostatic hypotension can result from Parkinson's disease itself and/or be secondary to dopaminergic drugs. The concomitant use of antihypertensives adds to this side effect of dopaminergic drugs. In some patients the symptoms of orthostatic hypotension are features of non-motor fluctuations and, thus, adjustment of antiparkinsonian medication will benefit these patients. The prescription of non-pharmacological treatments, such as water ingestion, raising the head of the bed and increasing salt ingestion, may be of benefit, even though evidence is lacking for the majority of these interventions [56]. The drugs most commonly used for orthostatic hypotension are midodrine, a selective peripherally acting α-adrenergic agonist and fludocortisone, a salt-retaining mineralocorticoid.

2.7.1 Midodrine

A systematic review [42] identified two level-1 placebo-controlled trials in a mixed population of patients, including Parkinson's disease. In both studies, midodrine was significantly superior to placebo in increasing blood pressure, but it was associated with supine systolic hypertension and cardiovascular adverse reactions. The heterogeneity of the samples in these studies did not allow any conclusions to be drawn on the efficacy of midodrine in Parkinson's disease.

2.7.2 Fludocortisone, etilefrine, L-threo-3,4-dihydroxyphenylserine and yohimbine

The same systematic review [42] as above identified one trial for each of the interventions fludocortisone, etilefrine and L-threo-3,4-dihydroxyphenylserine in small Parkinson's disease samples. According to the authors, the evidence was insufficient to support their use in Parkinson's disease. The results of one trial in 17 Parkinson's disease patients showed that yohimbine is nonefficacious for treating orthostatic hypotension in Parkinson's disease [42].

2.8 Gastrointestinal dysfunction

Several gastrointestinal abnormalities are experienced by late-stage Parkinson's disease patients, namely dysphagia, drooling, delayed gastric emptying and constipation, while others like small bowel malabsorption remain to be replicated [57,58]. The management of these gastrointestinal complications is aimed at the symptoms they cause, such as dysphagia, early satiety and abdominal discomfort and the interference they cause in levodopa pharmacokinetics. Therapeutic strategies to overcome disturbed levodopa pharmacokinetics are not the aim of this review.

2.8.1 Dysphagia

No controlled clinical trial has assessed the efficacy of pharmacological or non-pharmacological interventions for dysphagia in Parkinson's disease [59,60]. The insertion of a nasogastric or percutaneous gastrostomy tube is a common practice in late-stage Parkinson's disease, although no data are available regarding their effect on survival or quality of life.

2.8.2 Sialorrhea

2.8.2.1 Botulinum toxin

Lagalla *et al.* [61] investigated the safety and efficacy of 50 U of botulinum toxin type A (Botox®) in the treatment of sialorrhea in 32 Parkinson's disease patients in a double-blind, randomised, parallel, placebo-controlled trial. Botulinum toxin was injected into each parotid gland without using ultrasound guidance. Patients with dysphagia requiring soft food were excluded. Botulinum toxin was associated with a statistically significant reduction in drooling frequency, familial and social disability and saliva production compared to placebo. One patient treated with botulinum toxin complained of transient dysphagia. These results have been replicated in other trials [62-65]. A small study comparing ultrasound-guided versus 'blind' injection of botulinum toxin type A in parotid glands seemed to favour ultrasound-guided injections [66].

The efficacy and safety of botulinum toxin type B was evaluated in 16 Parkinson's disease patients in a double-blind, randomised, parallel, placebo-controlled trial [67]. Botulinum toxin or placebo was injected into each parotid gland (1000 U) and each submandibular gland (250 U) using anatomic landmarks. Patients injected with botulinum toxin reported a statistically significant improvement in drooling compared to placebo: the adverse events with botulinum toxin were mild and included a dry mouth (three patients), worsened gait (two patients), diarrhoea (one patient) and neck pain (one patient).

2.8.2.2 Anticholinergics

A randomised, double-blind, placebo-controlled, cross-over study in 17 Parkinson's disease patients investigated the benefit of sublingual ipratropium bromide spray [68]. Ipratropium bromide failed to show significant efficacy in the primary outcome, the weight of saliva production, compared to placebo, although it showed a mild effect in subjective measures of sialorrhea. There were no significant adverse events.

2.8.3 Delayed gastric emptying and constipation

2.8.3.1 Domperidone

One level-2 trial identified by a systematic review [42] found domperidone to be efficacious in reducing the duration of gastrointestinal emptying, in Parkinson's disease patients treated with levodopa.

2.8.3.2 Tegaserod

Tegaserod is an FDA-approved partial 5-HT_4 agonist for the short-term treatment of women with constipation from irritable bowel syndrome. A pilot, double-blind, randomised, parallel, placebo-controlled trial evaluated the efficacy and safety of tegaserod in 15 Parkinson's disease patients with constipation [69]. The results showed a trend for decreased

constipation in the active arm compared to placebo and a lack of adverse events with tegaserod.

2.8.3.3 Macrogol

Zangaglia *et al.* [70] tested the use of an isosmotic macrogol electrolyte solution for constipation in 57 Parkinson's disease patients, in an 8-week, randomised, double-blind, parallel, placebo-controlled study. The primary efficacy measure was the responder rate regarding constipation symptoms. Dietary habits and water ingestion were kept unchanged during the trial, in contrast to the intake of fibre. Withdrawals (n = 14) were higher with macrogol compared to placebo (31 versus 18%) and were not included in the final analysis. This analysis showed a statistically significant difference in the responder rates favouring macrogol ($p < 0.001$).

2.8.3.4 Cisapride

The use of cisapride has been associated with cardiac arrhythmias and sudden deaths and possibly aggravation of parkinsonism, which precludes its use in Parkinson's disease due to an unacceptable risk [42]. The US FDA has discontinued its use due to the risk of fatal arrhythmia.

2.9 Urological dysfunction

Urological problems in Parkinson's disease are usually associated with bladder dysfunction due to detrusor muscle hyperactivity, resulting in nocturia, urinary urgency and frequency and urge incontinence [71]. The overall approach should start by ruling out urinary tract infection and, in men, outflow obstruction by benign prostatic hyperplasia [71]. Anticholinergics are the most commonly used drugs for detrusor muscle hyperactivity, but no data based on controlled clinical trials are available regarding their use in Parkinson's disease [42,71].

3. Expert opinion

Late-stage Parkinson's disease stands at a phase of complex therapeutic management. Different phenomena can co-occur, namely severe motor impairment, predictable motor complications responsive to levodopa, unpredictable motor complications unresponsive to most available interventions, non-motor symptoms unresponsive to levodopa and with few efficacious alternative interventions and symptoms that endanger life such as dysphagia or, indirectly, bone fractures. Furthermore, drugs that benefit one condition (e.g., anticholinergics for urinary dysfunction) aggravate others in the same patient (dementia or psychosis). The first step in managing late-stage Parkinson's disease should be defining the therapeutic goal and respective outcome in an individual patient, knowing *a priori* this is a difficult and time- and cost-consuming task.

When facing a clinical diagnosis of Parkinson's disease dementia treatable causes should be excluded first (**Box 1**). If a work-up is negative, specific pharmacotherapy can then be tried using the acetylcholinesterase inhibitors rivastigmine or donepezil. Up to now rivastigmine has been the best-studied drug in Parkinson's disease dementia. Its mean effect is modest and long-term data extend to just 48 weeks. More evidence is necessary to support or refute long-term use beyond that time point. One should monitor the progression of dementia to establish when no further gains from acetylcholinesterase inhibitors are likely to occur, although stopping medication may be hampered by caregivers' expectations.

Similarly, the first step in treating psychosis is to search for treatable causes (**Box 2**) [72]. Drug-induced psychosis can occur even after small changes in medication, is typically dose dependent and, thus, usually ameliorates after dose adjustment or medication withdrawal. The last added drug should be the first to be reduced or withdrawn. The usual culprits are anticholinergics, selegiline or amantadine. Next, dopamine agonists should be reduced or eliminated: if psychosis persists, catechol-O-methyl transferase (COMT) inhibitors and controlled-released levodopa are then down-titrated or excluded. If still necessary, levodopa will be reduced, with the bedtime dose being first. Of note is that tricyclic antidepressants have an anticholinergic activity.

When specific treatment is warranted, low-dose clozapine is the best choice, though blood monitoring and potential dangerous side effects hamper its use. The usual doses of clozapine are < 25 mg/day, with many patients responding to 6.25 mg/day. We are aware that many experts do not consider clozapine as first-line treatment, based on the above safety issues and practicability and alternatively favour quetiapine. Present available data do question quetiapine efficacy and raise concerns about its safety. Therefore it cannot be recommended as a first-line drug until the matter is clarified, which might mean the definition of a proper dose. There is an urgent need for an efficacious antipsychotic without the risk of serious adverse events or aggravation of parkinsonism.

Falls in late-stage Parkinson's disease may derive from postural instability, gait problems, namely freezing, involuntary movements, syncope or postural hypotension and delirium or psychotic symptoms [41]. One should first identify which factor(s) most contribute to falls in a particular patient and then target the intervention accordingly.

If iatrogenic in origin, withdrawal of cause should be attempted. Reduce on period medication when dyskinesias and/or excessive mobility are the main cause of falls [41]. Reduce dopamine agonists when facing orthostatic hypotension or syncope and introduce specific non-pharmacological and pharmacological measures for orthostatic hypotension if necessary [41]. Reduce or stop drugs inducing delirium/psychosis and evaluate hypothetic dementia [41]. If falls are mainly caused by postural instability or freezing, increasing dopaminergic drugs should be tried, chiefly if the symptoms are mostly present during off periods [41]. Balance dysfunction may partially alleviate with increasing dosage of levodopa and off period freezing usually responds to levodopa [41]. Of note is that dopamine agonists were associated with an

Box 1. Management of Parkinson's disease dementia.

Review medication (special attention to anticholinergics)

Blood and urine work-up (including thyroid function tests, vitamin B_{12} and folic acid levels and exclusion of infection)

Neuroimaging (CT or MRI) to exclude structural lesions such as a subdural haematoma

If work-up negative use the acetylcholinesterase inhibitors rivastigmine or donepezil

Box 2. Management of psychosis.

Look for recent institutionalisation or home change

Blood and urine work-up to exclude infection, dehydration or metabolic imbalance

Look for falls: if appropriate, ask for neuroimaging (CT or MRI) to exclude structural lesions such as a subdural haematoma

Review recent change or adding in medication: start by adjusting dose of most recent changed/added drug

If no recent change, adjust the first anticholinergics selegiline or amantadine

Reduce or eliminate dopamine agonists

If psychosis persists, reduce or eliminate COMT inhibitors and controlled-released levodopa formulations

If necessary, reduce levodopa (bedtime dose first)

If insufficient, begin clozapine (6.25 mg) at bedtime and titrate accordingly: monitor blood and cardiac side effects

COMT: Catechol-O-methyl transferase.

increased frequency of freezing [41]. Further discussion on the treatment of freezing or postural instability is beyond the topic of this review.

Evidence suggests that, at best, physical rehabilitation, as a whole, is mildly effective with a transient benefit in improving freezing, gait mobility and falls. Training targeted at falls may be worth a try in non-demented patients. We may speculate whether passive movement of joints will by itself have some impact on survival, for instance by reducing pulmonary embolism: moreover, passive movement of joints is easily performed by caregivers at no cost. Other non-pharmacological interventions might reduce falls or the morbidity from falls, namely removing domestic hazards, using proper footwear and walking aids and reducing alcohol intake: in addition, the treatment of osteoporosis will reduce the incidence of bone fractures from falls (see below) [41].

Osteoporosis in late-stage Parkinson's disease can be effectively treated using alendronate or risedronate associated with vitamin D_2 or 1α-hydroxyvitamin D_3, but bedridden patients will no longer benefit from these drugs. However, since these drugs take more than 1 year to have an effect and the gastric upset decreases compliance, their effectiveness might be lower than the reported efficacy.

Abnormal postures of the limbs, neck and trunk frequently complicate late-stage Parkinson's disease. A correct differential diagnosis with other clinical entities should be the first approach, such as rheumatoid arthritis, Dupuytren's contracture, de Quervain's tenosynovitis of fingers, entrapment neuropathies, cervical myelopathies or babinski sign [51,73].

Joint deformities, such as striatal hand and foot, are unilateral as a rule and lack the typical local inflammatory signs of rheumatoid arthritis [73]. Some clinical features of striatal hand and foot overlap with other forms of dystonia and, thus, they must be differentiated from dystonia as a complication of pharmacotherapy and from those features associated with functional neurosurgery for Parkinson's disease [73]. In addition to typical striatal deformity, patients may develop severe flexion contracture of the fingers, leading to abrasion and secondary infection [73]. The rapid development of such contractures should bring attention to drug-induced reactive fibrosis in patients taking ergot dopamine agonists [73]. Striatal hand and foot may respond to levodopa and anticholinergics and some reports have described benefit with baclofen and benzodiazepines [73]. The preferred treatment is the injection of botulinum toxin in the affected muscles, namely in the lumbricals and short adductors of the thumb, though the benefit will depend on the severity of fixed contracture [73]. In more severe cases, orthopaedic surgery can be attempted and some authors have also reported benefit with thalamotomy [74].

A trial with levodopa or anticholinergics should be tried in patients with camptocormia or Pisa syndrome, who usually have a combination of rigidity and dystonia [51]. Patients with camptocormia and associated rectus abdominus contraction can transiently benefit from local injection of botulinum toxin [75]. In some, these postural deformities are secondary to cholinesterase inhibitors or antipsychotics, in which instances withdrawal of the offending drug is mandatory [76].

Pain in Parkinson's disease was found to be strongly associated with motor fluctuations (adjusted odds ratio 8.6 and 95% CI = 2.1 – 35.9) (p = 0.003) and dyskinesias (adjusted odds ratio 5.1 and 95% CI = 1.6 – 15.7) (p = 0.005) [54]. This association was true for dystonic- and non-dystonic-type pain, in particular musculoskeletal pain. There was also a significant correlation between the severity of pain and severity of motor complications. This same study found a lack of association between pain and medical diseases potentially associated with pain in the general population. Dystonic and non-dystonic pain were mostly reported during maximal disability (off period) and peak dose dystonia and during begin-dose or end-dose dystonia in a lesser frequency of cases [54]. In most cases, adjustments of levodopa

resulted in decreased dystonic and non-dystonic pain. Based on this and other reports [77,78], it is suggested adjusting dopaminergic medication as the first step in treating Parkinson's disease-associated pain. Patients with severe pain during an off period may also benefit from intermittent apomorphine or botulinum toxin injections [55].

In those patients not responding to dopaminergic drugs adjustment, an evaluation should be performed to rule out musculoskeletal and neuropathic/radicular pain, namely rotator cuff syndrome, frozen shoulder, cervical and lombar spondylosis and, less frequently, a cardiorespiratory disorder [52]. Therapy should then be directed accordingly [55]. When facing a suspicion of central or primary pain, the use of duloxetine is an option [52]. Where duloxetine is not a practical choice, a trial with tricyclics antidepressants or anti-epileptics could be tried.

Late-stage Parkinson's disease patients may also experience frozen shoulder, characterised by the insidious onset of pain, stiffness and loss of active and passive forward elevation and external rotation of shoulder [53]. The natural history is for recovery in ~ 30 months, but resolution may not be complete [53]. During the first, painful phase of disease, joint movements causing pain should be discouraged and NSAIDS can be given to alleviate pain [53]: patients benefit from intra-articular steroid injection, which is most effective when combined with physiotherapy and given early in the course of disease [79]. Physiotherapy alone is of limited value [79,80]. During the second, adhesive phase, treatment must focus on physiotherapy, and steroid injections are no longer indicated [53].

The management of orthostatic hypotension should start by checking whether patients are taking antihypertensives or α blockers to treat prostate hyperplasia. If so, a judicious decrease in its dose should be attempted [8]. Whenever possible, reducing the dose of agonists or, alternatively, of levodopa will be of help. An exception is made when hypotension symptoms are part of non-motor fluctuations, which implies adjustment of antiparkinsonian medication.

There is a lack of evidence to support the prescription of most non-pharmacological interventions for orthostatic hypotension in Parkinson's disease and, additionally, some of them are associated with low compliance (**Box 3**) [56,81-83]. With regard to water ingestion, it is known that the volume of ingested water influences the pressor response and that the pressor effect lasts for ~ 1 h [84,85].

When non-pharmacological interventions prove insufficient or non-compliant, pharmacotherapy should be started (**Box 4**) [56,81-83]. Although direct evidence is lacking, a first attempt with domperidone should be tried because of its additional effects on nausea, vomiting, gastroparesis and constipation. Midodrine should then be started and fludocortisone added later if necessary [81,82]. Midodrine is started at a dose of 2.5 mg/day and increased to a maximum of 10 mg, while fludrocortisone can be initiated at a dose of 0.1 mg/day and gradually increased [8]. Their use is best restricted to a dose in the early morning and early afternoon, when the symptoms are worst, taken 30 – 45 min before activity [8,56,81,82]. An important side effect is supine hypertension, especially at night and so it is critical to have supine blood pressure monitored [8,56,81,82,86]. Night-time supine hypertension worsens orthostatic hypotension because it induces pressure natriuresis, causing volume depletion [86]. In addition, it increases the risk of cardiovascular events and end-organ damage [86,87]. When severe, night-time supine hypertension requires treatment (**Box 4**) [81,82,86].

A recent trial, in a heterogeneous population of 58 patients with neurogenic orthostatic hypotension (including multiple system atrophy and pure autonomic failure patients), found pyridostigmine, alone or associated with midodrine, reduced orthostatic symptoms without causing supine hypertension [88].

Dysphagia is a dramatic concern, putting life in danger and so requiring a pragmatic intervention, even in the face of few available data. Non-pharmacological swallowing therapy by trained personnel could be tried. Some patients may improve with dopaminergic drugs, while anticholinergics should be withdrawn, as they were reported to worsen disphagia [89]. Insertion of a percutaneous gastrostomy tube to prevent choking and aspiration pneumonia and to tranquillise patients and caregivers is advisable when dysphagia becomes severe. One should inform patients and caregivers that oral feeding is still possible after gastrostomy (for example, to eat tasty food), as this seems to be a usual concern. Patients may suffer from other oesophageal abnormalities, such as non-peristaltic swallowing, segmental spasms, oesophageal dilatation and gastro-oesophageal reflux [90]. In these instances, dopaminergic drugs seem to offer no benefit and anticholinergics may again aggravate these symptoms, as oesophageal motility depends mostly on cholinergic mechanisms [91]. Other oesophageal symptoms, such as belching, can be related to motor fluctuations and may disappear during on periods [92].

Drooling saliva, as the result of inefficient and infrequent swallowing, is more prevalent in later stages of Parkinson's disease and during off periods [57]. In those patients whose dysphagia improves during on phases, dopaminergic drugs are a good first attempt to control drooling [57]. Otherwise, patients should be treated with botulinum toxin injections of either A or B serotype. If this is not feasible, sublingual administration of atropine ophthalmic solution could be tried before meals. This option prevents the systemic side effects and the aggravation of swallowing by oral anticholinergics. Tricyclic antidepressants, such as amitriptyline, in low doses at bedtime are another possible approach to sialorrhea.

Gastroparesis is an issue of major concern. The factors probably associated with it are food bulk, its composition in lipids and carbohydrates, constipation and

Box 3. Non-pharmacological interventions for orthostatic hypotension in late-stage Parkinson's disease.

Increase water ingestion, especially in the morning: this may worsen nocturia or urinary incontinence

Liberal salt intake with foods

Avoidance of sudden head up postural change and standing still for a prolonged period of time

Avoidance of prolonged recumbence during daytime: it is better to rest in a chair

Use of portable chairs during ambulation

Use of elastic abdominal binders and compression stockings (recommended to be thigh or waist high): stockings are associated with poor compliance

Soft exercise of leg and abdominal muscles, leg crossing and avoidance of straining during micturition and defecation

Small frequent meals with reduced refined carbohydrate content to prevent postprandial hypotension: restriction of alcohol

Avoidance of hot temperatures

During the night, lift the head of the bed to diminish nocturnal sodium loss and improve **OH** in the morning

Box 4. Pharmacological interventions for orthostatic hypotension in late-stage Parkinson's disease.

Start pharmacotherapy when non-pharmacological interventions are insufficient or non-compliant

Try domperidone first

Begin midodrine

Add fludocortisone later and, if necessary, monitor metabolic imbalances

Instruct patients taking pressor drugs not to lie down after each dose

Avoid pressor drugs intake in the evening and water boluses at bedtime

Monitor supine blood pressure, especially at night

If night-time supine hypertension give transdermal nitroglycerin, nifedipine, hydralazine or clonidine: clonidine also reduces nocturnal natriuresis

Box 5. Non-pharmacological and pharmacological interventions for gastroparesis and constipation in late-stage Parkinson's disease.

Eat small regular meals with avoidance of proteins during the day: take antiparkinsonian drugs during fasting

Diet rich in insoluble fibre

Avoidance of excessive gastric acidity

Use domperidone: attention to possible risk of QT prolongation and ventricular tachyarrhythmia

Try macrogol or tegaserod

Management of functional outlet obstruction: advise patients to evacuate during on periods or after taking a fast-acting agonist (e.g., apomorphine), increase dopaminergic drugs dose, try local injection of botulinum toxin and avoid use of laxatives

drugs such as dopamine agonists and anticholinergics [57]. Levodopa itself may aggravate gastroparesis, in cases where it remains in the stomach for too long, allowing dopa-decarboxylase to convert it to dopamine [93]. Non-pharmacological and pharmacological measures might ameliorate gastroparesis, some of them by promoting better levodopa absorption (**Box 5**) [57,94,95].

Constipation in Parkinson's disease is mainly due to poor colonic contractions and functional outlet obstruction or both (**Box 5**) [57,96]. The functional outlet obstruction seems to result from a pelvic floor off period dystonia and usually improves with an increase in the dose of dopaminergic drugs or a local injection of botulinum toxin [57,97].

In Parkinson's disease patients with urological symptoms, an accurate diagnosis is very important in order to prevent inappropriate urologic surgery [57]. In patients complaining of detrusor overactivity symptoms, that is nocturia, urgency, frequency and urge incontinence, a urinary tract infection must be ruled out [71]. Males may complain of bladder outflow obstruction symptomatology, such as hesitancy and poor flow, due to coexistent benign prostatic hyperplasia [57]. Urgency may also be a manifestation of obstruction, because this can cause secondary detrusor overactivity [57,71]. Having excluded infection and obstruction, cystometry may be used to demonstrate detrusor overactivity, but pharmacotherapy can be started based solely on symptoms (**Figure 1**) [71]. The postmicturition residual urine volume should then be measured by ultrasound, as the symptoms are poor predictors of the extent of incomplete emptying [71]. In cases refractory to treatment or in those with a persistently large postmicturitional residual volume an evaluation by an urologist is advisable [71].

In candidates for prostatic surgery, a cystometry is mandatory in order to document outflow obstruction and a trial of anticholinergics is reasonable if frequency symptoms are prominent [57]. One study with subcutaneous apomorphine showed a reduction in

Treatment options for non-motor symptoms in late-stage Parkinson's disease

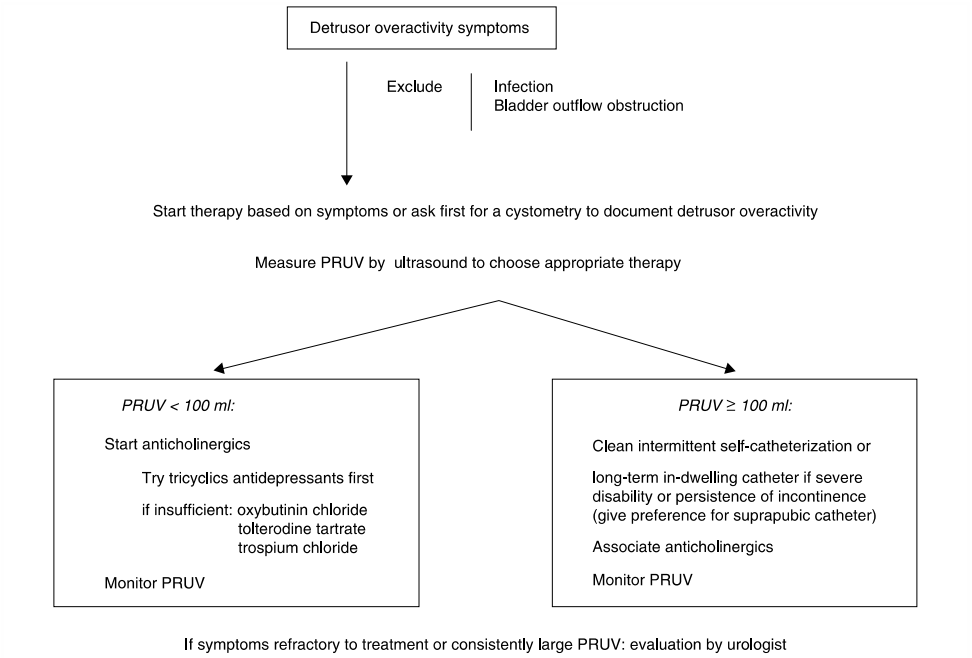

Figure 1. Management of detrusor overactivity. Start therapy based on symptoms or ask first for a cystometry to document detrusor overactivity. Measure the postmicturition residual urine volume (PRUV) by ultrasound to choose appropriate therapy. If the symptoms are refractory to treatment or there is a consistently large PRUV an evaluation by a urologist is needed.
PRUV: Postmicturition residual urine volume.

outflow obstruction symptoms, suggesting this could be used to test the reversibility of the obstruction before prostatic surgery [98].

Some Parkinson's disease patients also develop a hypoactive detrusor, causing difficulty in initiating micturition, incomplete bladder emptying and urinary leakage [8]. These patients could be started on α blockers, such as terazosin (1 – 5 mg at bedtime), doxazosin (1 – 8 mg at bedtime), alfuzosin (2.5 mg three times a day) or tamsulosin (0.4 – 0.8 mg in the morning) [8]. However, these drugs may exacerbate orthostatic hypotension.

Declaration of interest

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